UNIVERSITY OF STIRLING

INSTITUTE OF BIOLOGICAL SCIENCES

The Importance of Aggregation in the Dynamics of

Host-Parasite Interaction in Wildlife:

A Mathematical Approach

Thesis submitted for the degree of Doctor of Philosophy

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September 2003

Contents

Statement of Originality

I hereby acknowledge that this Ph.D. dissertation is solely based upon original work carried out by myself and has no been submitted for consideration previously for a higher degree at this or any other University. Any references henceforth used have been appropriately acknowledged.

Roberto Rosà

May 2003

Acknowledgements

The first person I would like to thank is Peter for presenting me with the opportunity to undertake this research and for supervising me throughout the majority of my Ph.D. I am grateful for his many helpful comments, suggestions and invaluable proof reading of this thesis.

I am also very grateful to Peter's family, especially to Mary, who made me welcome in their home when this journey began three years ago.

I would also like to thank my supervisors Mike Boots and Rachel Norman for all their help and support. I wish Rachel all the best with her new baby, the third one!

Special thanks to Annapaola for encouraging me to start this Ph.D. and to Gianni Nicolini and Claudio Chemini, at the Centro di Ecologia Alpina, who gave me the freedom to complete this Ph.D.

I would like to acknowledge the great help of Andrea for introducing me to Mathematical Biology and for his precious guidance and helpful suggestions over the course of these many years.

A special thanks goes to Nicola who shared many weekends with me in the Department during our visits to Stirling and endured many walks to and from Lyon Crescent in the bloody Scottish rain!

I am also grateful to all the other students and staff in the Department who have made my time here enjoyable and helped to support my nomadic lifestyle in Stirling. So, thanks to Isa, Sarah, Marie, Jo, Kate, Sarah, Gemma, Jenny, Andrew, Alan, Andy, Jonathan, Scott and all the other people I met during these three years in Scotland.

Special thanks to friends and colleagues at the Centro di Ecologia Alpina, especially the people of the 'gruppo topi' - Fausta, Stefania, Valentina, Giovanna, Javier, Anna, Silvia, Sonia and all the other people who work and tolerate life in such a unique place.

Another very special thank you must go to my parents and family without whom I would never have got this far.

Finally, a special warm thanks to Silva who has supported me and especially sopported me (it's Italian, it means to put up with me!) over the last two years. She is the only person who is able to make me really happy even though she has not a clue what $a+b-c=0$ means!

Thanks again to everyone.

Abstract

This study examines, from a modelling point of view, the dynamics of infectious diseases in wildlife caused by macroparasites and by tick-borne infections. The overall aim was to investigate the important role played by parasite aggregation in the dynamics of both systems.

For macroparasites we first developed some deterministic models that incorporate explicit mechanisms for generating aggregation in parasite distribution, specifically multiple infections and host heterogeneity. We explored the role of aggregation in host regulation and in determining a threshold value for parasite establishment. A large aggregation makes it more difficult for parasites both to regulate hosts, and to get established in a population at carrying capacity. Furthermore, the stabilization yielded by aggregation strongly depends on the mechanism that produces the aggregation.

We then introduced some uncertainties into the host-macroparasite system, presenting an individual-based stochastic model that incorporated the same assumptions as the deterministic model. Stochastic simulations, using parameter values based on some real case studies, preserved many features of the deterministic model, like the average value of the variables and the approximate length of the cycles. An important difference is that, even when deterministic models yield damped oscillations, stochastic simulations yield apparently sustained oscillations. The amplitude of such oscillations may be so large as to threaten the parasites' persistence.

With respect to tick-borne diseases we presented a general model framework that incorporated both viraemic and non-viraemic routes of infections. We compute the threshold for disease persistence and study its dependence on the parameters and on host

densities. The effects of tick aggregation and correlation between different tick stages on the host have both an important effect on infection persistence, if non-viraemic transmission occurred.

In the case of Lyme Disease and Tick-borne Encephalitis (TBE) in Trentino (northern Italy) we showed some numerical results, using parameter estimates based on a detailed field study, and explored the effects of uncertainty on the endemic equilibrium of both diseases assuming only viraemic transmission for Lyme Disease while for TBE we permitted only non-viraemic transmission through co-feeding ticks.

In conclusion we have examined the patterns and changes of aggregation in a number of contrasting systems and believe that these studies highlight both the importance of considering heterogeneities in modelling host-parasite interactions and, more specifically, modelling the biological mechanisms that produce aggregation in parasite distributions.

1. General Introduction

1.1 Mathematical models for infectious diseases

Mathematical models have had a very important role in the development of our understanding of epidemiology (Hethcote, 1990; Anderson and May, 1991; Grenfell and Dobson, 1995; Hudson *et al.*, 2002).

A primary reason for disease modelling is that it leads to clear statements about the assumptions concerning the biological mechanisms that influence the temporal and spatial spread of pathogens. Model formulation is particularly valuable to epidemiologists since it forces workers to be precise about the relevant aspects of disease dynamics. Principal advantages of mathematical models for infectious diseases is the clarity and precision of mathematical formulation. A model using difference, differential, integral or functional differential equations is not ambiguous or vague. Of course, the parameters must be defined precisely and each term explained from basic principles, but the resulting model is a definitive statement of the assumed mechanism involved. Once the mathematical formulation is complete, there are many mathematical techniques available for determining the threshold, equilibrium, periodic solutions and their local and global stability. Thus the full power of mathematics is available for the analysis of equations and providing a clear understanding of disease dynamics. The mathematical analysis and computer simulation can identify important combinations of parameters and essential aspects or variables in the model that allows not only understanding but also the potential ways and means of controlling infectious diseases.

When formulating a model for a particular disease, it is necessary, to decide which biological features are essential and need to be included to explore a specific question but also to make the models simple by omitting a number of parameters. Simple models have the advantage that they have only few parameters, but they have the disadvantage of possibly being naïve. Complex models may be more realistic, but they may also require estimates for many parameter values. The art of epidemiological modelling is to make suitable choices in the model formulation so that it is as simple as possible and yet is adequate for the question being considered. It is important to recognize both the capabilities and limitations of epidemiological modelling. Many important questions cannot be answered using a given class of models. The most difficult problem for a modeller is to find the interesting question and the right combination of data and a mathematical model which can answer the question.

Epidemiological modelling can also play an important role in exploring and examining epidemiological theory. Mathematical and computer simulation models are fundamental experimental tools in epidemiology that can be used to make predictions and answer "What if?" questions. Experiments with infectious diseases in natural population are often unethical or very expensive or impractical and modelling provides the means of making explorative predictions. Furthermore, the analysis of mathematical models can lead to the introduction of new concepts that turn out to play a vital role. An example of this was the identification of the critical threshold for epidemic development (the basic reproduction number, R_0).

Another reason for using epidemiological models is to make forecasts about the future trends of the disease dynamics and the role of diseases in regulating and influencing the dynamics of host populations. Thus, they are an important tool for planning, implementing and evaluating detection, control and prevention programs. Although empirical workers

may often think of prediction as the primary or as the only purpose of epidemiological modelling, the reasons cited above may be more important. Accurate forecasts are usually not possible because of the idealization in the model and the uncertainty in the parameter values. However, possible forecast under various scenarios can sometimes be given or trends can be identified.

After discussing the purposes and advantages of epidemiological modelling, it is imperative to also discuss the limitations. Epidemiologists and policy makers need to be aware of both the strengths and weakness of the epidemiological modelling approach.

The first and most obvious limitation is that all epidemiological models are simplifications of reality. For example, it is often assumed that the population is uniform and homogeneously mixing, but this may not be an important assumption for some diseases depending on the circumstances. This deviation from reality is rarely testable or measurable; however, it can sometimes be estimated intuitively from an understanding of the biology of the pathogen-host system.

The modeller must be aware that as the complexity of a model increases so it approaches reality but as the number of parameters increases so it becomes increasingly difficult to estimate values of all of these parameters and there are problems with the error terms being multiplicative. Thus the modeller must make many decisions regarding the relevant aspects in choosing a model for a specific disease or question.

When describing the reasons for the application of epidemiological models one thinks primarily of deterministic models since they are simpler and have traditionally been more widely used, even with the development of more sophisticated stochastic models.

Deterministic models are those which use difference, differential, integral or functional differential equations to describe the changes in time of the variables included in model. Given the starting conditions for a well-posed deterministic epidemiological model,

the solutions as a function of time are unique. In stochastic models, there are transition probabilities at each step of moving from one population state to another. When these models are simulated with the probabilities calculated using random number generators and error distributions so the outcomes of different runs are different.

Simple deterministic models for epidemics have a precise threshold which determines whether an epidemic will occur or will not occur. In contrast, stochastic models for epidemics yield quantities such as the probability that an epidemic will occur and the mean time to extinction of the disease. Thus the approach, concepts and appropriate questions are quite different for stochastic models.

Both deterministic and stochastic epidemiological models have other limitations besides being only approximations of reality. Deterministic models do not reflect the role of chance in disease spread and persistence. Sometimes parameter values in deterministic models are set equal to the mean of observed values and the information on the variance is ignored. A set of initial conditions lead to exactly one solution in a deterministic model; thus no information is available on the reliability or the confidence in the results. Some understanding of the dependence on parameter values is obtained through a sensitivity analysis where the effect of changes in a single parameter values on the final outcome can be examined. A parameter in a model is said to be sensitive if small changes in the parameter lead to big changes in the results. Stochastic models incorporate changes, but it is harder to get analytical results for these models. Moreover, computational results are also harder since simulations could require many computer runs in order to detect patterns and get quantitative results.

Recently, with the development of high-speed computers, individual-based simulation models are becoming increasingly popular; some recent examples that examine host-parasite interactions include Wilber and Shapiro (1997) and Peters and Lively (1999).

In an individual-based model, the characteristics of each individual are tracked through time. This stands in contrast to modelling techniques where the characteristics of the population are averaged together and the model attempts to simulate changes in these averaged characteristics for the whole population.

In individual-based simulation models, one can easily introduce many important factors missing from simple deterministic models, such as spatial structure with local interaction, genetical and behavioural differences among individual hosts. If the rules of simulation models are very complex, it becomes however difficult to disentangle the effect of the different factors, and to reach the qualitative understanding yielded by deterministic models.

In this thesis I consider models for wildlife diseases caused by macroparasite and by tick-borne infections following both a deterministic and an individual-based stochastic approach.

1.2 Macroparasite models

Anderson and May (1978) defined two types of parasite which have different epidemiological features. Microparasites include bacteria and viruses and characteristically increase rapidly in number when introduced into a susceptible host, and there is little point in considering the precise number of infective agents that an infected host harbours. In this case compartmental models are traditionally used that class individuals in the population as either susceptible, infected or immune.

On the other hand macroparasites, which include helminths (worms) and arthropods, are parasitic species for whom reproduction usually occurs via the transmission of free-living stages that pass from one host to the next. Direct reproduction rarely occurs within the definitive host, although asexual reproduction can occur in the intermediate

hosts (Hudson *et al.*, 2002). Infections tend to be chronic, leading to morbidity rather than mortality. An individual host's mortality and morbidity will generally increase with the number of parasite it harbours. It is then important to measure and consider not only the prevalence of infection (i.e. the proportion of infected hosts) but also the mean parasite burden as well as the whole distribution of parasites among hosts (Gulland, 1995; Hudson and Dobson, 1995) since fertility, mortality and behaviour of the host population will depend on how parasites are distributed among hosts. The process of reinfection will be an usual and important event in the interaction of hosts and parasites.

Much of our current understanding of the interactions between macroparasites and their hosts is based on the simple deterministic models presented by Anderson and May (1978). They examined the importance of host heterogeneity in the dynamics of host-parasite interactions, especially in relation to the possible influence this would have in aggregating parasites in a few hosts (See Section 1.4 for a wide treatment of these concepts). Following the application of the negative binomial distribution to fit empirical data on parasite abundance, they were able to obtain a simple system of differential equations describing host-macroparasite dynamics, which was the basis for several predictions about the possibility of host regulation by parasites, and of sustained oscillations of hosts and parasites. This model has been the basis of a large development of empirical and theoretical literature, reviewed for instance in Grenfell and Dobson (1995) and Hudson *et al.* (2002).

Many other factors have been considered in macroparasite models such as seasonality (White *et al.*, 1996), multi-species and/or trophic levels (Grenfell, 1992; Begon and Bowers, 1995) and immunity (Woolhouse, 1992; Grenfell *et al.*, 1995a). Other factors, that can be considered important for parasite dynamics and evolution, such as host spatial

structure and genetical diversity (see, for instance, the respective chapters in Grenfell and Dobson, 1995), have rarely been integrated into models for macroparasites.

1.3 Tick-borne infections models

Vector-borne diseases cause serious human health problems throughout the word. The high mortality caused by malaria, for instance, represents one of the most serious problems for public health in many parts of poorer tropical areas of Africa, Asia and Latin America. Tick-borne diseases, such as Lyme Disease and Tick-Borne Encephalitis (TBE), have become an important problem to human population in more temperate regions including parts of Europe, the former USSR and North America.

Tick-borne disease systems incorporate interesting complexities due to the presence of a number of heterogeneities in the system coupled with non-linear phenomena operating in the transmission processes between ticks, host and pathogen (Randolph *et al.*, 2002).

This complexity has required the development of several mathematical models for either tick-borne infections, or tick population dynamics The important first step was to develop mathematical models for tick population dynamics (e.g. Sandberg *et al.*, 1992; Kitron and Mannelli, 1994; Randolph and Rogers, 1997). The second step was to develop models for tick-borne infections and these have often been set, for ease of analysis, in continuous time: see, for instance, Hudson *et al.* (1995) and O'Callaghan *et al.* (1997). Norman *et al.* (1999) and more recently Gilbert *et al.* (2001) proposed a model where ticks are subdivided in the three stages (larvae, nymphs and adults) with stage progression only through a blood meal on a vertebrate host (two types of which are considered in the model), and transmission is only viraemic (i.e., from infected host to susceptible tick if there enough virus in the blood of the host, and vice versa). A very similar model has also

been studied by Caraco *et al.* (1998), while qualitatively similar results have been obtained by Van Buskirk and Ostfeld (1995) and Mannelli (in press) in computer-based models.

In a number of tick-borne systems, workers have demonstrated that certain tick hosts, which do not produce a viraemic response, i.e. do not have enough virus in their blood for transmission directly to ticks, will permit non-viraemic transmission between co-feeding ticks (Jones *et al.*, 1987; Labuda *et al.*, 1993; Odgen *et al.*, 1997). Randolph *et al.* (1996, 1999, 2002) have shown the importance of co-feeding (transmission between ticks feeding together on an incompetent host) and temporal coincidence of different tick stages in the maintenance of TBE. For these systems it may be necessary to consider this non viraemic transmission specifically, particularly if it crucial to the persistence of the disease (Randolph *et al.*, 2002; Perkins *et al.*, in press).

1.4 Parasite aggregation in host-parasite systems

The causes and consequences of parasite aggregation in host-parasite interaction continues to be a lively research area. In terms of data analysis, many studies have discussed the widely observed pattern of aggregated distributions of parasites within a host population. Recent studies have improved the methodology for analyzing aggregation in parasite data (Rousset *et al*., 1996; Wilson *et al*., 1996; Wilson *et al*., 2002).

Many other studies have focused on the causes and population dynamic consequences of the pattern of parasite distribution among hosts. These studies have often used mathematical models as theoretical tools for detecting the consequences of parasite distribution on the dynamics of host-parasite interaction.

In this section, we discuss these relevant aspects of host-parasite systems reviewing the most important studies in the parasitological literature.

1.4.1 Aggregation in the data

Aggregation is a very widespread phenomenon in ecological populations (Taylor, 1961; Anderson *et al.*, 1982; Shaw and Dobson, 1995). Aggregation is characterized by the estimated variance to mean ratio. A variance equal to the mean would indicate a completely random (Poisson) distribution of individuals within the sampled population but if the estimated variance to mean ratio is significantly greater than unity, the distribution is aggregated, i.e. individuals tend to be clumped in sampling units.

The importance of aggregation to the dynamics of animal populations in general has been the focus of much theoretical work. For example, in insect populations, spatial aggregation has been shown to enhance density-dependent processes, provide potential refuge for prey, and allow apparently competing species to co-exist in the same habitat (Hassell *et al.*, 1991).

The distribution of macroparasites between hosts is also characteristically aggregated. The degree of aggregation can be measured in a number of ways. One statistical distribution that is extensively used to describe parasite aggregation is the negative binomial distribution, which has two parameters: the mean of parasite burden and a parameter k that is an inverse measure of aggregation. The lower is k, the more aggregated is the distribution; on the other hand, when k goes to infinity, the distribution tends to a Poisson, the prototype "random" distribution.

This general use may bring about the situation where parasite burdens are *de facto* assumed to fit the negative binomial distribution. In human parasite infections, this assumption has been examined in detail and found to be justified (Anderson and May, 1982; Anderson and May, 1991; Bundy and Medley, 1992).

A broad review regarding animal-parasite infections was carried out by Shaw and Dobson (1995) where many host-parasite frequency distributions obtained from a literature

review of different parasite infections in wildlife has been analysed. Most parasites (mainly helminths) were found to be aggregated with respect to their hosts and the relationship between log mean of parasite burden and log variance was found to be remarkably consistent. The aggregated nature of the parasite infections was also apparent from other measures of aggregation such as the prevalence-mean relationship and the negative binomial parameter *k*.

Shaw *et al.* (1998) analysed the same frequency distributions performing a maximum likelihood estimate of the degree of parasite aggregation. In all cases, the fit of the dataset to the negative binomial distribution was compared to the fit to the Poisson distribution. They found that the negative binomial distribution provided a better fit than the Poisson distribution and in terms of goodness of fit, in more than 90% of the data-sets the negative binomial distribution provided a statistically satisfactory fit. The degree of aggregation was large, in most cases the estimated *k* was less than 1. This excellent fit to the negative binomial distribution was despite the many differences between the systems: diversity in host types, host habitat and parasite taxonomic class. In addition, the high degree of aggregation estimated is in agreement with reviews on human-parasite infections (Anderson and May, 1978; Bundy and Medley, 1992; Guyatt *et al.*, 1990).

Ectoparasites, in particular ticks, are also found to be aggregated with respect to their hosts. In fact, tick stages (larvae, nymphs and adults) show highly aggregated distributions on their host, e.g. rodents (Randolph *et al.*, 2002; Perkins *et al.*, in press). We shall examine this later, since this pattern might have extremely important effects on pathogen transmission in some tick-borne diseases.

1.4.2 Biological sources of aggregation

Heterogeneity has become a very important and widely used term in ecology and epidemiology. Following Chesson and Murdoch (1986) it is defined in terms of the

variation in risk of parasitism between different individuals in the host population. A particular form of heterogeneity of risk arises when, at any one time, parasitism is confined to part of the host population, with the remaining hosts protected from parasitism in some kind of refuge. These refuges may take several forms. There may be spatial refuges when parasitism is confined to part of the habitat; there may be temporal refuges depending on the timing and overlap of the different host and parasites stages; or some host phenotypes may act as a refuge by completely escaping from parasitism (Hassell, 2000). All these heterogeneities are likely to generate aggregated distributions of parasite among their hosts.

In this study I explored a number of biological conditions under which an aggregated distribution, in particular a negative binomial distribution, could arise.

Variation in parasitism rates associated with the heterogeneities in the host population includes host age, sex, behaviour and body condition together with genetic and immunological factors.

Host age

A number of empirical studies have reported different relationships between parasite burden and host age (Anderson and Gordon, 1982; Anderson and May, 1985; Pacala and Dobson, 1988). Recent theoretical studies of parasite aggregation have focused on mathematical models for the development of aggregation with host age (Grenfell *et al.*, 1995a; Isham, 1995; Quinnell *et al.*, 1995). The relationship between parasite intensity and host age, usually described with an age-intensity curve, might show a continual increase in parasite load or a gradual levelling-off of parasite burden with host age. For other host-parasite systems the age-intensity curve is convex; in other words, rather than rising to asymptote, parasite load declines after an initial increase (Hudson and Dobson, 1995;

Wilson *et al*., 2002). These different epidemiological patterns are highly specific to the host-parasite system under study, and may vary between populations.

Quinnell *et al*. (1992) observed that mean parasite burden of nematodes in mice increased asymptotically with host age, whereas Anderson and Gordon (1982), Pacala and Dobson (1988) and later Gregory *et al*. (1992) found for different parasite infestation in animal populations that mean intensity exhibited a convex age-intensity profile.

There are a number of different mechanism that might account for convex age-intensity curve. These include parasite-induced host mortality, acquired immunity, age-related changes in predisposition to infection, age-dependent changes in exposure to parasites and age-related probabilities of accurately determining parasites loads (Wilson *et al*., 2002).

Acquired immunity develops in response to accumulated experience of infection and acts to decrease parasite establishment, survival, reproduction and maturation. Although acquired immunity is believed to be an important factor causing convexity in the age-intensity curves for macroparasite infections in humans (Anderson and May, 1991) and domesticated and laboratory animals (Lloyd and Soulsby, 1987; Dobson *et al*., 1990), there have been few clear demonstration of acquired immunity in wildlife (Quinnell *et al*., 1992).

Host sex

Epidemiologists have long recognized that males of vertebrate species, including humans, tend to exhibit higher rates of parasitism and disease than females (Bundy, 1988; Zuk, 1990; Wilson *et al*., 2002; Moore and Wilson, 2002). There are a number of biological mechanisms potentially capable of generating sex biases in parasitism rates. Often these causes are divided into ecological and physiological mechanisms. Ecological mechanisms include sex differences in behaviour, diet composition and body size.

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Physiological mechanism includes sex differences in the levels of a number of steroid hormones, such as testosterone, progesterone and oestrogen. All of these hormones are known to have direct or indirect effects on components of the immune system and/or on parasite growth and development (Grossman, 1985; Harder *et al*., 1992; Hillgart and Wingfield, 1997). The production of hormones and the interaction between these hormones and the immune response may differ between the sexes.

Even if sex biases exist, and are relevant, determining the relative importance of the different mechanisms capable of generating them may prove extremely difficult, due to the fact that many ecological and physiological factors covary (Wilson *et al*., 2002).

Host body condition

Host response to parasitic infection is likely to be costly. In particular, body condition is likely to affect the hosts' ability to compensate for damage inflicted by parasites, such as repairing tissue or replacing critical nutrients. Hosts in poor condition are therefore in a difficult situation: they have few resources available to spend on defence, but they cannot afford not to invest in the defence since the parasite may induce more severe disease. This situation should affect the distribution of the whole range of parasites within a host population. If differences in host body condition are of importance in generating observed infection patterns in animal population, we may therefore expect intensities of different parasite species to covary (Wilson *et al*., 2002).

Host behaviour

By definition, parasites affect the fitness of their hosts. Therefore, natural selection will favour individuals that evolve effective behavioural strategies to reduce the contact rate with the infective stage of parasites or their vector. If individuals differ in their behaviour, then this can generate heterogeneities in parasitism rates (Wilson *et al*., 2002). Behavioural strategies for avoiding parasitism or minimizing their impact are many and

varied. For vertebrates these include grooming, grouping, selfish herding, migrating, avoidance of infested or infected conspecifics and fly-repelling behaviour (Hart, 1994; 1997).

Genetic and immunological factors

Genetic and immunological factors are on the basis of parasite resistance in natural host populations, likely to play a primary role in determining the parasite distribution within their hosts (Quinnell and Keymer, 1990; Grenfell *et al.*, 1995b). The ability of the host immune system to respond to a stimulus is strictly correlated with the host genetics but other factors can influence the efficiency of this response such as the intensity of this stimulus (number of parasites, frequency of encounters between host and parasites, etc.) and the host fitness (trophic availability, stress condition, etc.). In spite of that, genetic heterogeneity of natural populations is one of the most important factors that influence the host-parasite interaction both at individual and population level.

External heterogeneities

Finally we consider those heterogeneities that do not fall neatly into those that are attributes of the host and parasites. These include the spatial distribution of parasite's infective stages in the environment and seasonal variation in infection levels.

The rate of acquisition of new infection often increases with the frequency of contact between the host and infective stages. Thus, if there is spatial variation in the density of free-living infective stages, and different hosts utilize different parts of the environment, then this will often lead to heterogeneities in parasites intensity across the host population (Wilson *et al.*, 2002). A good set of experiments on invertebrates carried out by Keymer and Anderson (1979) illustrated that infection through free-living stages with a uniform distribution cause a lower level of aggregation in the distribution of adult parasite within hosts respect to infection with infective stages that are spatially aggregated.

Temporal variation in parasite loads and aggregation appears to be common (Shaw and Dobson, 1995; Shaw *et al*., 1998; Scott, 1987). These variations can be generated by variation in both host physiology (e.g. immune function) and host exposure to parasites infective stages. The latter is often due to the fact that the mortality and the development rate of the free-living stages are temperature-dependent and sensitive to seasonal variation in humidity.

1.4.3 Effects of aggregation on host-parasite dynamic

The interaction of the distribution and dynamics of parasites on hosts has been considered from a variety of theoretical angles in recent years (Hassell and May, 1973; Anderson and May, 1978; Anderson and May, 1985; Pacala and Dobson, 1988; Adler and Kretzschmar, 1992; Kretzschmar and Adler, 1993; Rosà and Pugliese, 2002). A theme throughout much of the discussion has been the causes and consequences of the widely observed pattern of aggregated distributions of parasites, data which have traditionally and successfully been fit by the negative binomial distribution. Several reasons have been proposed, generally falling into the broad categories of host heterogeneities and dynamical factors.

Here, we concentrate on the dynamical consequences of such distributions on the dynamical properties of host-parasite interactions.

The classic paper of Anderson and May (1978) considered in detail the stability of the system in which parasites regulate their host population by increasing mortality of heavily infected hosts. To deal with the problem of the distribution of parasites among host, they assumed that the distribution retains a particular shape regardless of the mean number of parasite per host. They contrast the regular positive binomial distribution, the aggregated negative binomial distribution with fixed clumping parameter *k*, and the random (Poisson) distribution, finding that the positive equilibrium, where host and

parasite coexist, is unstable in the first case, stable in the second and neutrally stable in the last. This result confirms previous findings from insect host-parasite models by Hassell and May (1973), that parasite aggregation is an important factor in the dynamics of host-macroparasites interactions and it seems to be relevant in stabilizing the dynamics towards an equilibrium coexistence.

Adler and Kretzschmar (1992) and Kretzschmar and Adler (1993), showed that stability in models of this form is determined not by the degree of dispersion itself, but by the dependence of dispersion on the mean of parasite burden. They postulated that a 3-dimensional model including the dispersion (variance to mean ratio) as a dynamical variable more accurately approximates the dynamics of host-parasite interaction in comparison with the 2-dimensional model introduced by Anderson and May (1978).

More recent models (Rosà and Pugliese, 2002), which incorporate explicit mechanisms for generating aggregation, have shown that the stabilization yielded by aggregation depends strongly on the mechanism producing the aggregation.

In particular, multiple infections (in any infection a host ingests more than one free-living stages) are much less stabilizing than when aggregation is assumed to be fixed as in Anderson and May model, while the opposite holds when aggregation is produced by host heterogeneity. In these models, the role of aggregation on host regulation and in determining a threshold value for parasite establishment has also been explored (See Chapter 2 for the details of these models).

Many theoretical models of host-parasite associations are also used to analyse the population dynamics of competition between parasites (Dobson, 1985; Dobson and Roberts, 1994; Gatto and De Leo, 1998). The analysis of these models, where parasites species are assumed to exhibit a negative binomial distributed, suggests that one of the most important factor allowing competing species of parasites to coexist is the statistical

distribution of parasites within the host population. As each species becomes more aggregated in its distribution, the importance of interspecific competition decreases and population regulation becomes more dependent upon intraspecific interactions. The statistical distribution of the different parasite species is therefore at least as important a component of the competitive interaction, as are different patterns of resource and nutrients utilization.

However, more recent models have identified that in two macroparasite one host systems, models that do not use the negative binomial approximation for describing the parasite distribution (Pugliese, 2000) lead to completely different results regarding the coexistence of the two parasite species.

As previously mentioned, tick stages also show highly aggregated distribution on their host (e.g. rodents), and these aggregated distributions are coincident rather than independent (Perkins *et al.*, in press); those hosts which were feeding larvae were simultaneously feeding the greatest number of nymphs.

As a result, about 20% of hosts feed about three-quarters of both larvae and nymphs and the number of susceptible larvae feeding alongside potentially infected nymphs is twice as many as it would be if the distribution were independent (Randolph *et al.*, 2002; Perkins *et al*., in press).

This pattern might have extremely important effects on pathogen transmission in many tick-borne diseases (e.g. Tick-Borne Encephalitis). In fact, tick aggregation on hosts and correlation of tick stages facilitate co-feeding transmission (transmission between ticks feeding together on the same host) and thus significantly increase the basic reproductive number R_0 of the pathogen with direct implication on the persistence of the disease in the system (Randolph *et al.*, 1996; 1999; 2002) (See Chapter 4 for the details of this system).

1.5 Aims and objectives

The objective of all the work reported in this Thesis was to improve the general understanding of the important role played by parasite aggregation in the dynamics of host-parasite interaction looking at different systems such as macroparasitic infections and tick-borne infections.

The main method was to produce mathematical models for capturing both the causes and consequences of aggregation.

Initial work concentrated on exploring, through different modelling approaches, the role of macroparasite aggregation in host regulation and in determining threshold values for parasite establishment. Numerical simulations, using parameter values based on some case studies, were performed to obtain some clues on what can be inferred about real host-parasite interactions.

This effort was extended to tick-borne infections where the effects of tick aggregation on hosts and correlation of tick stages on the persistence of tick-borne disease were explored. Also in this case, the parameterisation of the model was performed for a couple of case studies concerning tick-borne disease in Trentino (Northern, Italy).

The overall aim of this work was to obtain general conditions for long-term persistence of infection caused by macroparasite and by tick-borne pathogens, focusing the attention on the role plays by parasite aggregation. These results may be used for implementing and evaluating detection control and prevention programs in different host-parasite interactions in wildlife.

1.6 Overview of the Thesis

The first chapter is a general Introduction in which we present some purposes and limitations of epidemiological modelling. Afterwards we describe in detail the kind of

models considered in this Thesis, these are models for host-macroparasite interactions (both deterministic and individual-based stochastic models) and models for tick-borne infections (only deterministic models). In addition, we make an extensive review of the parasitological literature concerning the widely observed pattern of aggregated distribution of parasites within the host population, describing in particular the causes and the population dynamic consequences of this pattern of parasite distribution among hosts.

In Chapter 2 we review the models for macroparasites of Anderson and May (1978) and compare them with some more recent deterministic models (Rosà and Pugliese, 2002) focusing attention on the role played by the aggregation in host regulation and in determining a threshold value for parasite establishment.

In Chapter 3 we introduce some uncertainties in the host-macroparasite system presenting an invividual-based model that may be considered the stochastic counterpart of the deterministic models introduced in Chapter 2. The stochasticity considered in this chapter is intrinsic to the discrete nature of populations and is often called "demographic stochasticity". From the results of simulations we can detect how well the predictions of the deterministic models hold for simulation models and to understand the phenomena brought in by "demographic stochasticity".

In Chapter 2 and 3 we performed, deterministic and stochastic simulations using parameter values based on three sets of parameters concerning different macroparasitic infections in wildlife. The first is the well known red grouse (*Lagopus lagopus scoticus*) - *Trichostrongylus tenuis* system in northern England (Dobson and Hudson, 1992), the second is the infection by Trichostrongylidae in a chamois (*Rupicapra rupicapra* L.) population in the Brenta mountain group (northern Italy) (Rosà *et al.*, 1997) and the third concerns the *Ascaridia compar* infection in rock partridge (*Alectoris graeca saxatilis*) in Trentino region (northern Italy) (Rizzoli *et al.*, 1997; Rizzoli *et al.*, 1999).

In Chapter 4 we present a general model for tick-borne infections and derive an explicit formula for the threshold for disease persistence in the case of viraemic transmission only, and in the case of both viraemic and non-viraemic transmission. This model also allows for aggregation and correlation of tick stages, as a result of a hosts' heterogeneity in tick infestation and permits us to see the effect of this kind of host's heterogeneity on the long-term persistence of the disease in the system.

In Chapter 5 we apply the tick-borne disease model of Chapter 4 to a couple of case studies in Trentino (Northern Italy): Lyme Disease and Tick-Borne Encephalitis (TBE).

Finally, in Chapter 6, an overview of the study is made, where results are summarised, connected, and discussed in a global context, and where the final conclusions may be found.

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Chapter 2

Aggregation, Stability and Oscillations in Different Models for

Host-Macroparasite Interactions

Theoretical Population Biology 61:319-334 (2002)

by

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2.0 Abstract

Aggregation is generally recognized as an important factor in the dynamics of host-macroparasites interactions and it has been found relevant in stabilizing the dynamics towards an equilibrium coexistence. In this paper we review the models of Anderson and May (1978) and compare them with some more recently developed models, which incorporate explicit mechanisms (multiple infections or host heterogeneity) for generating aggregation, and different degrees of mathematical accuracy. We found that the stabilization yielded by aggregation depends strongly on the mechanism producing the aggregation: multiple infections are much less stabilizing than when aggregation is assumed to be fixed from the outside, while the opposite holds for host heterogeneity. We also give analytical estimates of the period of oscillations occurring when the equilibrium is unstable. Finally, we explore in these models the role of aggregation in host regulation and in determining a threshold value for parasite establishment.

2.1 Introduction

Much of our current understanding of the interactions between macroparasites and their hosts is based on the simple deterministic models presented by Anderson and May (1978). They understood the importance of host heterogeneity in the dynamics of host-parasite interactions, especially in causing most parasites to be aggregated in few hosts. Furthermore, following the use of the negative binomial distribution to fit empirical data on parasite abundance (Bliss and Fisher, 1953; Crofton, 1971), they summarized aggregation as a single parameter, k, from the negative binomial distribution; this parameter is relatively easy to estimate empirically. In this way they were able to obtain a simple system of differential equations describing host-macroparasite dynamics, which

was the basis for several predictions about the possibility of host regulation by parasites, and of sustained oscillations of hosts and parasites.

This model has been the basis of a large development of empirical and theoretical literature, reviewed for instance in Grenfell and Dobson (1995) and Hudson *et al.* (2002). Many other factors have been considered in macroparasite models such as seasonality (White *et al.*, 1996), multi-species and/or trophic levels (Grenfell, 1992; Begon and Bowers, 1995), immunity (Woolhouse, 1992; Grenfell *et al.*, 1995). We remark instead that factors considered to be very important for parasite dynamics and evolution, such as host spatial structure and genetical diversity (see, for instance, the respective chapters in Grenfell and Dobson, 1995), have rarely been integrated in models for macroparasites.

On the other hand, there are two main problems in introducing a fixed aggregation parameter k in the model. First of all, k is not a parameter corresponding to some biological process, but is instead a population statistics; hence, a certain value of the aggregation parameter k may correspond to different biological mechanisms, which may also cause k to fluctuate in time. Main suggested mechanisms for maintaining aggregation (see Gross and Ives, 1999, for a recent review on the same problem for parasitoids) are differences in the susceptibility to parasites among hosts (Anderson and May, 1991), immunoepidemiological interactions (Grenfell *et al.*, 1995), or multiple infections (Quinnell *et al.*, 1995; Isham, 1995). It might well be that different mechanisms producing aggregation cause different host-parasite dynamics.

The second problem is mathematical; the models by Anderson and May (1978) are based on the introduction of the negative binomial distribution in an infinite system of differential equations, introduced by Kostizin (1934), describing the immigration and death of parasites in hosts. However, the exact distribution in the infinite system is certainly

different from negative binomial (Pugliese *et al.*, 1998); hence, the models by Anderson and May (1978) can be regarded only as an approximation of a more complex model.

In the many years following the appearance of Anderson and May (1978), other approaches have been followed: the analysis of the infinite system itself (Kretzschmar, 1993), the introduction of different approximations (Adler and Kretzschmar, 1992; Kretzschmar and Adler, 1993), the integration of a mechanism creating aggregation (multiple infections) into a dynamic population model (Pugliese *et al.*, 1998).

It seems important to investigate whether the results of Anderson and May (1978) are robust through all these different approaches and assumptions. Indeed, it has been found out recently that, for models of two macroparasite species on one host, simplified models using the negative binomial approximation (Dobson, 1985; Dobson and Roberts, 1994; Gatto and De Leo, 1998) lead to completely different results as for species coexistence than the infinite-dimensional model (Pugliese, 2000).

We review here these modelling approaches, and compare, qualitatively and quantitatively, their results, restricting the attention to models that consider only the basic processes of a host-parasite interaction: infections, and births and deaths of hosts and parasites.

In Section 5 we let parasite fertility and mortality depend on within-host parasite density, as suggested by some empirical evidence (Smith and Grenfell, 1985; Hudson and Dobson, 1997); however, this kind of density-dependence has been considered only in a model presented by Hudson and Dobson (1997), and no extensive study on its effect on host-parasite dynamics has been accomplished.

2.2 Models

2.2.1 Main assumptions

As stated above, only the biological processes necessary to a basic description of the interactions of a macroparasite species with its host will be considered here. To keep models as simple as possible, we deal only with parasites with direct life cycle and infections occurring through free-living larvae or eggs. The main variables of interest will be N, the number of hosts, and P, the total number of adult parasites. All free-living stages will be grouped in a single stage, L, neglecting any time delay between release of eggs from adult parasites and development of infecting stages. Laws assumed for new infections, and the other relevant processes (parasite deaths, and hosts' births and deaths) are summarized in Tab. 1.

TABLE 1. Summary of symbols and laws.

Variable or rate	Used in models	Symbol
Number of hosts		N
Total number of adult parasites		P
Number of free-living stages	with free-living stages explicit	L
Aggregation of parasite distribution (variance to mean ratio)	with variable aggregation	A
Birth rate of a host carrying i parasites	with linear law	$b-\xi i$
	with multiplicative law	$b(1-\xi)^i$
Death rate of a host carrying i parasites	with linear law	$d+\alpha i$
Density-dependent increase in host mortality	with logistic effects	ν
Carrying capacity for hosts	with logistic effects	$N_K=(b-d)/\nu$
Death rate of adult parasites	with linear law	$\sigma+i\sigma_B$
Parasite fertility	with multiplicative law	$h(1-r)^i$
Death rate of free-living stages		δ
Probability of parasite establishment		ψ
Rate at which hosts pick up infecting stages	using free-living stages	βL
	neglecting free-living stages	$\dfrac{h\sum i(1-r)^i p_i}{c+N}$ with $c=\delta/\beta$
Aggregation parameter	with fixed aggregation	k
Mean number of free-living stages per "parcel"	with multiple infections	λ

Infections occur through encounters between hosts and infecting stages at the rate proportional to their product (Tab. 1); in other words, we may say that the rate φ at which one host becomes infected is equal to $\beta\psi L$, where β is the encounter rate, and ψ is the probability of parasite establishment.

Apart from infections, host and parasites will be assumed to be subjected only to births and deaths. We will disregard delays and arrestments in the development of parasite larvae, as considered for instance in Dobson and Hudson (1992), and assume that all larvae that get established in a host immediately become adults. Hence, a model will be specified when parasites and hosts' fertilities and mortalities will be prescribed as functions of the numbers of hosts and parasites. In most models, mortalities and fertilities of adult parasites are assumed to be constant, σ and h, respectively, independently of how many parasites and hosts are present. See Section 5 below for different assumptions.

On the other hand, death and birth rate of hosts will depend on how many parasites a host harbours; following Anderson and May (1978), we will assume here that death rate of hosts increases linearly with the number of parasites. Note that, if the parasite-induced death rate α is equal to 0, there is no effect of parasites on hosts' death rate. A different assumption («threshold» law) has been used by Bouloux *et al.* (1998): in its simplest version, mortality of a host is constant, below a certain threshold value of parasites; above the threshold value, mortality jumps to a high value.

Anderson and May (1978) assumed that also birth rate of a host would decrease linearly with the number of parasites harboured. A consequence of this assumption is that a host with a very high parasite burden would have a negative birth rate. In order to avoid this incongruity (however, for realistic parameter values, the frequency of such pathologies would be extremely low), Diekmann and Kretzschmar (1991) assumed a multiplicative

effect of parasites on birth rate. Finally, natural birth (*b*) and death (*d*) rates may be assumed to depend on host population size, to simulate logistic effects.

The natural variables to describe completely the system are $p_i(t)$, the number of hosts carrying *i* parasites. Since a new infection moves a host from the *i-1* class into *i*, and, vice versa, death of an adult parasite moves a host from *i+1* class into *i*, one arrives, performing all the book-keeping, to an infinite system of differential equations in the variables $p_i(t)$, first introduced by Kostizin (1934):

$$\begin{cases} \dfrac{dp_0(t)}{dt} = -(d + v\sum_{i=0}^{\infty} p_i(t))p_0(t) - \beta\psi L(t)p_0(t) + \sigma p_1(t) + b\sum_{i=0}^{\infty} p_i(t)(1-\xi)^i \\[2mm] \dfrac{dp_i(t)}{dt} = -(d + v\sum_{i=0}^{\infty} p_i(t))p_i(t) - \alpha i p_i(t) - \sigma i p_i(t) - \beta\psi L(t)p_i(t) + \sigma(i+1)p_{i+1}(t) + \beta\psi L(t)p_{i-1}(t) \quad \text{i}\geq 1 \\[2mm] \dfrac{dL(t)}{dt} = h\sum_{i=0}^{\infty} ip_i(t) - \delta L(t) - \beta L(t)\sum_{i=0}^{\infty} p_i(t). \end{cases} \quad \text{(Inf+L)}$$

The number of hosts, *N(t)*, and of parasites, *P(t)*, relate to $p_i(t)$, as:

$$N(t) = \sum_{i=0}^{\infty} p_i(t), \quad P(t) = \sum_{i=0}^{\infty} ip_i(t).$$

From system (Inf+L), one arrives at the following equations for *N(t)* and *P(t)*:

$$\frac{dN}{dt} = -(d + vN)N - \alpha P + b\sum_{i=0}^{\infty} p_i\xi^i$$

$$\frac{dP}{dt} = -(d + vN + \sigma) + \varphi N - \alpha\sum_{i=0}^{\infty} i^2 p_i.$$

(1)

It is possible to obtain a law for the infection rate, neglecting the larval phase altogether, as in Anderson and May (1978):

$$\varphi = \frac{h\psi P(t)}{c + N(t)},$$

(2)

with $c = \delta/\beta$. Equation (2) is a good approximation if the expected duration of all free-living stages is much shorter than the expected lifetime of hosts and adult parasites. In any case, it provides a simpler model against which the effect of time delays can be assessed.

2.2.2 The negative binomial approximation

Note that (1) is not a closed system of differential equations, since the terms

$\sum_{i=0}^{\infty} p_i \xi^i$, $\sum_{i=0}^{\infty} i^2 p_i$ are not expressed in terms of the variables *N(t)* and *P(t)*. As for the

infection rate φ, we can either use (2) or the rule $\varphi = \beta \psi L$ and then add the equation for the

free-living larvae *L(t)*.

The idea of Anderson and May (1978) was to impose that $p_i(t)$, are distributed

according to a negative binomial of aggregation parameter *k*. As well known, the lower is

k, the more aggregated is the distribution; on the other hand, when *k* goes to infinity, the

distribution tends to a Poisson, the prototype "random" distribution. From *N(t)* and *P(t)*,

one computes the mean parasite load, *x(t)=P(t)/N(t)*; then, since the negative binomial

distribution has two parameters, and the other, *k*, is fixed, one can obtain all $p_i(t)$, and then

can "close" system (1). Using *x(t)* as variable, instead of *P(t)*, one obtains the following

systems, with and without the free-living stages equation:

$$
\begin{cases}
\dfrac{dN}{dt} = N\left(b\left(\dfrac{k}{\xi x + k}\right)^{k} - d - \nu N - \alpha x \right) \\[2ex]
\dfrac{dx}{dt} = \beta \psi L - x\left(b\left(\dfrac{k}{\xi x + k}\right)^{k} + \sigma + \alpha + \dfrac{\alpha}{k}x \right) \\[2ex]
\dfrac{dL}{dt} = hNx - \delta L - \beta L N.
\end{cases}
\qquad \text{(Fix k+L)}
$$

$$
\begin{cases}
\dfrac{dN}{dt} = N\left(b\left(\dfrac{k}{\xi x + k}\right)^{k} - d - \nu N - \alpha x \right) \\[2ex]
\dfrac{dx}{dt} = x\left(\dfrac{h\psi N}{c + N} - b\left(\dfrac{k}{\xi x + k}\right)^{k} - \sigma - \alpha - \dfrac{\alpha}{k}x \right).
\end{cases}
\qquad \text{(Fix k)}
$$

Models (Fix k) and (Fix k+L) are not precisely those used by Anderson and May (1978)

but incorporate the multiplicative law for parasite-induced reduction of fertility of

Diekmann and Kretzschmar (1991), with a change in the meaning of the parameter ξ. The system may appear rather complex, but when there is no reduction of fertility ($\xi = 0$) it reduces to a very simple form. Also note that these models have one extra parameter, k, with respect to the infinite system.

This procedure of approximation can be brought one step further, as shown by Adler and Kretzschmar (1992). From the second-order moment equations, one can obtain a differential equation for the aggregation index $A(t)$ (variance over mean of the distribution) which will involve the third moment. Then, assuming that $p_i(t)$, are distributed according to a negative binomial whose parameters are specified by $x(t)$ and $A(t)$, one obtains a four-dimensional system in the variables $N(t)$, $x(t)$, $A(t)$ and $L(t)$:

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - vN - \alpha x) \\[2mm]
\dfrac{dx}{dt} = x(-\sigma - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) + \beta \psi L \\[2mm]
\dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{\beta \psi L}{x}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}} \\[2mm]
\dfrac{dL}{dt} = hNx - \delta L - \beta LN.
\end{cases}
\qquad \text{(VarA+L)}
$$

Neglecting the free-living stage explicitly, one obtains the three-dimensional system (VarA) shown in Appendix.

The difference between (Fix k) and (VarA) is that in the former, aggregation is fixed by choosing the parameter k, while in the latter aggregation will vary over time according to the processes that influence it. It has been shown (Damaggio and Pugliese, 1996) that (VarA) actually produces very little aggregation, and the same seems to be true for the infinite system: indeed, the aggregation present at the equilibrium of the infinite system arises through the mixing of age classes differing in mean parasite burden (Pacala and Dobson, 1988), while the distribution of each age class is Poisson (Pugliese, 2000).

Thus, all these systems seem to be somewhat lacking: (Fix k) does not let aggregation vary in time, and does not provide any way of understanding how and why aggregation arises in the first place; on the other hand, the aggregation produced by the infinite system and (VarA) is much too low with respect to empirical patterns.

2.2.3 Multiple infections

A model that provides a reasonable degree of flexibility has been introduced by Pugliese *et al.* (1998). In that model, aggregation in the distribution of adult parasites arises mostly from multiple infections (see also Barbour and Kafetzaki, 1993; Isham, 1995). Within this model, it is assumed that, in any infection, a host ingests a random (according to a truncated Poisson law of parameter λ) number of free-living stages; from this assumption ("parcels of larvae"), one obtains the infinite system (InfClump+L) shown in Appendix. Using the same procedure as above, one then arrives at the following system:

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - vN - \alpha x) \\[2mm]
\dfrac{dx}{dt} = x(-\sigma - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) + \beta\psi L \\[2mm]
\dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{\beta\psi L}{x}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}} + \dfrac{\beta\psi L}{x}\lambda \\[2mm]
\dfrac{dL}{dt} = hNx - \delta L - \beta LN.
\end{cases}
\qquad \text{(VarAClump+L)}
$$

Neglecting the free-living stage explicitly, one obtains the system (VarAclump) shown in Appendix.

Note that (VarA) is simply a special case of (VarAClump) with $\lambda=0$. No simple identification holds with (Fix k) instead, since they differ in the parameters: (Fix k) has aggregation described by the parameter k; (VarAClump) has a mechanism ($\lambda>0$) creating aggregation. Nonetheless, it is tempting to compare them, equating small k with large λ. Finally, when looking for analytical approximations of quantities of interest, it is sometimes convenient to consider a particular version of (VarAClump+L) that assumes a

fixed aggregation; while Anderson and May assumed k to be constant, in the approximation (FixA+L) we keep instead $A(t)$ at its equilibrium value A^*. System (FixA+L) often is a better approximation of the infinite system than (Fix k+L), and it allows to compute an approximation of the period of cycles, as shown below. The equations of (FixA+L) are shown in Appendix.

2.2.4 Heterogeneity in host susceptibility

Anderson and May (1991), as well as many other authors, suggest that differences among hosts in predisposition to infection are the main reason for the aggregation of parasite distributions empirically observed. This could be caused by different level of host immunity against the parasite. Acquired immunity, if protective, may act to limit the establishment of parasite, their rate of development, their fecundity and their survival (Grenfell and Dobson, 1995).

We consider here a very simple model that takes account of this kind of heterogeneity in the host population. However, to keep the model simple, we do not consider acquired immunity but assume that heterogeneity is innate, so that hosts are born in one susceptibility class, and keep that class forever; moreover, the class in which an individual is born is independent of that of its parents.

Precisely, we assume here that the probability of parasite establishment is ψ_1 for hosts of type 1 and ψ_2 for hosts of type 2. Furthermore, q_j is the proportion of individuals born in class j, where clearly $q_1+q_2=1$. Introducing the variables $p_{i,j}(t)$, that represent the number of hosts of type j carrying i parasites, one obtains the system (InfHet+L) shown in Appendix.

We will not consider any approximation based on this model. Instead, we will compare the behaviour of system (InfHet+L) to that of the systems (Fix k+L) or (VarAClump+L),

approximations obtained under other assumptions, to study how important is the mechanism determining aggregation to the dynamics of host-parasite systems.

2.3. Comparisons among different models

2.3.1 Quantitative agreement

In Figures 1 and 2 we present some numerical simulations of the infinite system together with its low-dimensional approximations.
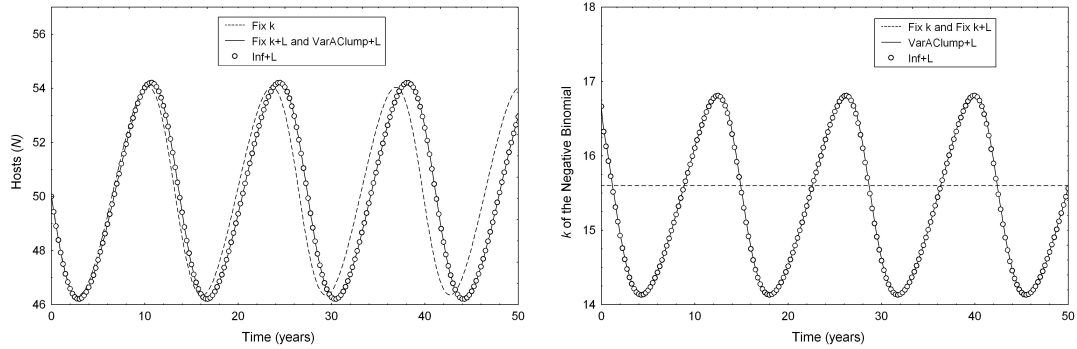

FIG. 1. Comparison between truncated infinite model (Inf+L) (*i_max*=70) and lower-dimensional models for host population (*N*) and the parameter *k* of the negative binomial distribution in the case $\lambda=0$. The other parameters are *b*=0.6, *d*=0.5, ν=8.3e-04, α=1.8e-03, *h*=100, ψ=0.5, σ=4, β=0.12, ξ=0.01, δ=60, *k*=15.6.
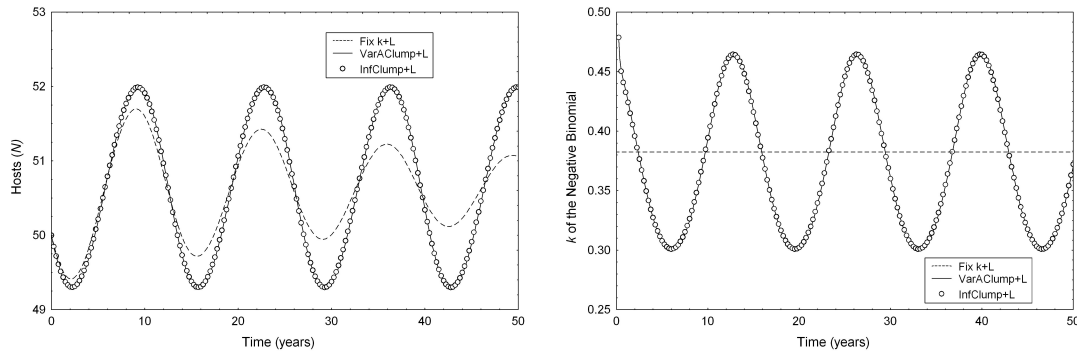

FIG. 2. Comparison between truncated infinite model (InfClump+L) (*i_max*=200) and lower-dimensional models for host population (*N*) and the parameter *k* of the negative binomial distribution in the case $\lambda>0$. The parameter values are *b*=0.6, *d*=0.5, ν=8.3e-04, α=1.8e-03, *h*=100, ψ=0.5, σ=4, β=0.12, ξ=0.01, δ=60, *k*=0.38, λ=40.

In Fig. 1 we consider the basic version of (Inf+L), compared to (VarA+L) and (Fix k+L) while in Fig. 2 we used the version with multiple infections (InfClump+L) that results in a system with much more aggregation, compared to (VarAClump+L) and (Fix k+L).

Models (Inf+L) and (VarA+L) [or (InfClump+L) and (VarAClump+L)] have the same parameters; hence, there are no problems with the comparisons. On the other hand, model (Fix k+L) contains the parameter k not present in the infinite systems; hence, we used, in both cases, for system (Fix k) the average value of k resulting from numerical computation of the infinite system in the same way as an experimenter would use the value of k resulting from estimates of actual data. It can be seen that, in both cases, the models (VarA+L) [or (VarAClump+L)] are an excellent approximation of the corresponding infinite system (actually the two curves are indistinguishable in these figures); as for (Fix k+L), it works very well (except, of course, that k is constant, instead of variable as in the infinite system) when there is little aggregation (Fig. 1), while the approximation is not perfect and actually yields a qualitatively different result (damped vs. sustained oscillations) when the aggregation of the parasite distribution is high, i.e. k is less than one (Fig. 2).
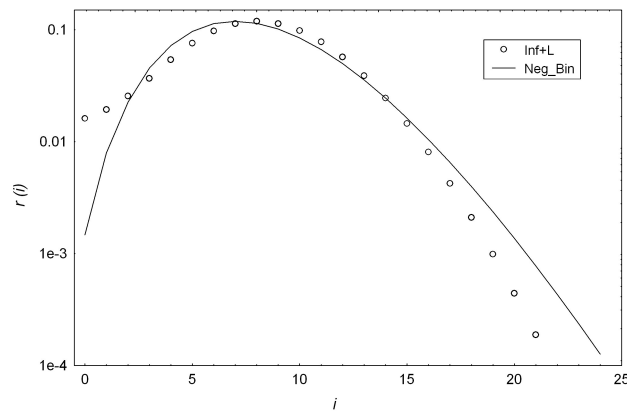

FIG. 3. Comparison between the distribution of $r_i=p_i/N$ and the best-fit negative binomial when the host population reaches the first maximum in Fig. 1.

The mechanism underlying such a good agreement between (InfClump+L) and (VarAClump+L) is not yet understood; indeed, the simulated distribution of the infinite system appears rather different from negative binomial (Fig. 3, noting however the logarithmic scale). How does the model with host heterogeneity compare to the approximate models (VarAClump+L) or (Fix k+L)? Now the approximations are based on a different mechanism than the one present in the infinite model (InfHet+L); hence we cannot expect a perfect agreement between the two. Again, we compared models from the point of view of an experimenter that does not know of the heterogeneity in susceptibility but tries to fit models (VarAClump+L) or (Fix k+L) to observed data on average parasite load and aggregation; precisely; we chose the values of λ (respectively of k) that predict average values comparable to those of (InfHet+L). We present in Figures 4 and 5 (corresponding to different parameter values) simulations of (InfHet+L) together with (VarAClump+L) or (Fix k+L).

FIG. 4. Comparison between truncated infinite model with host heterogeneity (InfHet+L) (*i_max*=300) and lower-dimensional models for host population (*N*) and the parameter *k* of the negative binomial distribution. For (InfHet+L) ψ_1=1, ψ_2=0.025, q_1=q_2=0.5, for (VarAClump+L) ψ=0.5 and λ=15, for (Fix k+L) ψ=0.5 and k=0.93. The other parameters are b=0.6, d=0.5, ν=8.3e-04, α=1.8e-03, h=100, σ=4, β=0.12, ξ=0.01, δ=60.

It can be seen that the average values of the different systems indeed are very similar (the parameter values have been chosen to this purpose), but the qualitative pattern of solutions are rather different. In Fig. 4 there are very quickly damped oscillations for

(InfHet+L), sustained oscillations for (VarAClump+L) and (Fix k+L) is intermediate. In Fig. 5 there are sustained oscillations both for (VarAClump+L) and (Fix k+L) while damped oscillations for (InfHet+L).
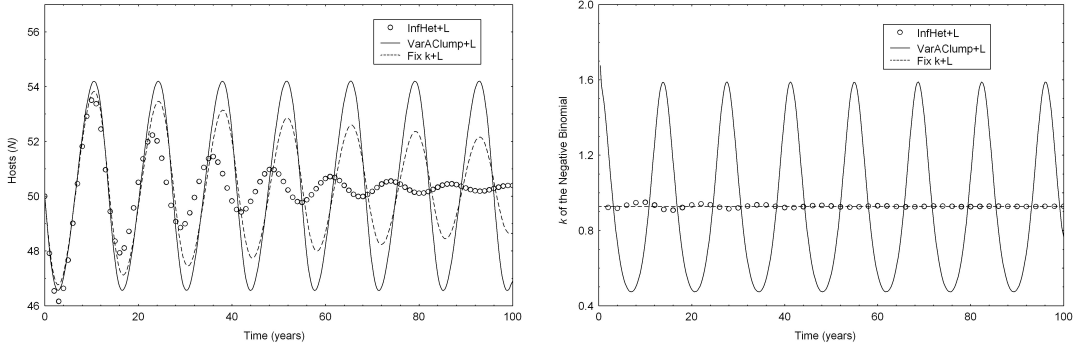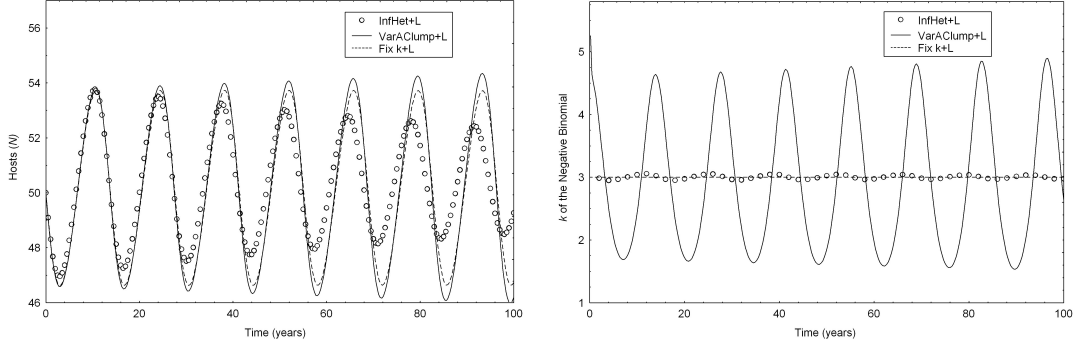

FIG. 5. Comparison between truncated infinite model with host heterogeneity (InfHet+L) (*i_max*=300) and lower-dimensional models for host population (*N*) and the parameter *k* of the negative binomial distribution. For (InfHet+L) ψ_1=0.75, ψ_2=0.25, q_1=q_2=0.5, for (VarAClump+L) ψ=0.5 and λ=4, for (Fix k+L) ψ=0.5 and *k*=3. The other parameters are *b*=0.6, *d*=0.5, ν=8.3e-04, α=1.25e-03, *h*=100, σ=4, β=0.12, ξ=0.01, δ=60.

2.3.2 Conditions for host regulation

The rest of this Section is devoted to a qualitative comparison among the approximate models (little is known analytically about the infinite models). We found (or took from the literature, when available), for each model, the conditions on the parameters for some interesting features: host regulation, thresholds for parasite establishment, for multiple stable states, for sustained oscillations. Some of these conditions are listed in Tabs. 2 and 3 or shown in the following figures. We discuss each feature in more detail, starting from the conditions for host regulation.

TABLE 2. Host regulation conditions for the examined models.

Model	Condition
Inf	$1 > b\int_0^\infty e^{-da}\exp\left\{-\frac{h\psi(b-d)}{\sigma+\alpha}\left[a-\left(\frac{1-e^{-(\sigma+\alpha)a}}{\sigma+\alpha}\right)\right]\right\}da$
Fix k	$h\psi > b+\sigma+\alpha+(b-d)/k$
VarA	$(h\psi-(b+\sigma+\alpha))(2h\psi-b) > b(b-d)$
VarAClump	$(h\psi-(b+\sigma+\alpha))(2h\psi-b) > b(b-d)+\alpha\lambda h\psi$

Anderson and May (1978) first showed that parasites might regulate a host population, in the sense that, although the host population would grow exponentially in absence of parasites (no density-dependence), it is possible that, in the presence of parasites, the population settles to an equilibrium. Indeed, this is possible in all models considered; in Tab. 2 we show the conditions found for host regulation in each model; to make expressions simpler, we assumed that there is no effect of parasites on host fecundity ($\xi = 0$). We see that, as intuitively expected, host regulation is easier when parasite fertility, h, is high, when host fertility, b, and parasite mortality, σ, are low. Less intuitively, it is easier when pathogenicity, α, is low (but not zero) and aggregation is low (k is large for (Fix k) or λ is low for (VarAClump)).

TABLE 3. Basic reproduction ratio (R_0) of the parasite and the multiple equilibria thresholds for the examined models.

Models	R_0	Multiple equilibria
Inf	$\dfrac{h\psi N_K}{c + N_K}\dfrac{1}{b + \sigma + \alpha}$	$\xi > \dfrac{\alpha}{b + 2(\alpha + \sigma)}$
Fix k	$\dfrac{h\psi N_K}{c + N_K}\dfrac{1}{b + \sigma + \alpha}$	$\xi > \dfrac{\alpha}{bk}$
VarA	$\dfrac{h\psi N_K}{c + N_K}\dfrac{1}{b + \sigma + \alpha}$	$\xi > \dfrac{\alpha}{b + 2(\alpha + \sigma)}$
VarAClump	$\dfrac{h\psi N_K}{c + N_K}\dfrac{1}{b + \sigma + \alpha A_K}$	$\xi > \dfrac{\alpha\,(\exp(1/B) - 1)}{A_0 - 1}$ [*]

[*] A_0 and B are complex functions of the parameters of the model defined in Pugliese *et al.* (1998)

Comparing the models, we see that (Fix k) with no aggregation ($k = +\infty$) does not give the same condition as (VarAClump) with $\lambda = 0$; in the former case, host regulation occurs for $h\psi > b + \sigma + \alpha$, while in the latter it is somewhat more difficult. Finally, the condition for host regulation in the infinite system is definitely hard to interpret, although the effect of parameters is analogous.

We remark that in real populations other factors may control the host; by and large, we may say regulation from parasites will occur when the level at which the population would be brought considering only interactions with parasites is lower than the carrying capacity resulting from trophic interactions. In this sense, the results obtained for exponentially growing hosts can give insights also for more realistic cases.

2.3.3 Thresholds for parasite establishment

It makes sense to consider a threshold for parasite establishment, only if a carrying capacity for hosts exists; in fact, in all these models, any kind of parasite would be able to get established into an infinite population, as it would occur assuming hosts' exponential growth in absence of parasites. Thus, we assume a carrying capacity N_K for hosts (Tab. 1), and find the conditions under which the equilibrium with N_K hosts and no parasites is unstable; its instability means that, if we introduce a small number of parasites in a population close to the carrying capacity, the number of parasites will initially increase and therefore they will be able to get established in the population. The instability conditions can be stated in terms of a threshold quantity (R_0) to be larger than 1; the quantity R_0 is called basic reproductive ratio and can often be interpreted as the average number of adult parasites produced by an average adult parasite over its life (Diekmann *et al.*, 1990).

The quantities R_0 for the various models are listed in Tab. 3. It can be seen that they are identical for models (Inf), (Fix k) and (VarA), while that for (VarAClump) is somewhat lower. The agreement between (Inf) and (VarA) confirms the excellence of the approximation in this respect too; unfortunately, there is no explicit formula for the threshold of (InfClump), so that we can not compare it with the threshold for (VarAClump). The lower R_0 for (VarAClump) depends on the fact that multiple infections result in hosts being infected with more than one parasite, even when parasites are very sparse; thus the death rate of a host harbouring a parasite will be on the average equal to

$d+\alpha A_K$, where $A_K > 1$ is the average aggregation when parasites are very rare (Pugliese *et al.*, 1998); this effect is consistent with the fact that aggregated parasites are less capable of regulating a host population. In this respect, it is actually surprising (it seems a defect in the approximation) that the threshold for (Fix k) is always identical to that of (VarA) and (Inf) and does not vary with the aggregation level *k*.

2.3.4 Thresholds for multiple stable states

Diekmann and Kretzschmar (1991) found that, when parasites have a multiplicative effect on fertility, host regulation may lead not to a unique equilibrium, but to multiple equilibria. Under these conditions, what is called a catastrophe becomes possible, i.e. a small change of parameter values may yield a big change in equilibrium values. The computations are obtained using bifurcation theory (Kretzschmar, 1993; Pugliese *et al.*, 1998) in models with exponential growth of hosts. From the results shown in Tab. 3, we see that this phenomenon may occur only if the fertility reduction induced by parasites (ξ) is large enough. One can also see a difference (already remarked in Kretzschmar, 1993) between (Inf) and (VarAClump) on one side and (Fix k) on the other; in fact, in (Inf) and (VarAClump), for each combination of the other parameters, it is always possible to find ξ large enough to give rise to multiple equilibria (however, the values of ξ necessary for this may be unrealistically high); on the other, since ξ cannot be larger than 1, multiple equilibria will be impossible when aggregation is large (*k* small enough) in (Fix k) approximation. Multiple stable states probably exist (under more stringent conditions on parameters) also when hosts grow under a logistic law, although this has been rigorously shown only in a modification of (Fix k) (Pugliese and Rosà, 1995).

2.3.5 Stability of the endemic equilibrium

As already noted by Anderson and May (1978), in macroparasite models there is a tension between stabilizing and destabilizing processes: the former are density-dependence

in host population growth, parasite-induced host mortality and aggregation in parasite distribution; destabilizing processes are, citing only the ones including in the present paper, parasite-induced reduction of host fertility, and the length of the life span of free-living stages. When only stabilizing [destabilizing] processes are relevant, the endemic equilibrium will be stable [unstable], whereas when both kinds of processes are present, stability will depend on the exact values of parameters.

The same qualitative effects occur in all the models considered. Therefore, the conclusion about stabilizing and destabilizing processes is robust to modelling details.

As for the quantitative relevance of parameters, the conditions for stability are somewhat complex: it seems more useful showing the stability boundaries in parameter regions than writing down explicitly the conditions. To make things simple, we plot, for a few values of the aggregation parameters, the maximum value of fertility reduction ξ (Fig. 6) and the minimum value of larval death rate δ (Fig. 7) against pathogenicity, α, such that the endemic equilibrium is stable.

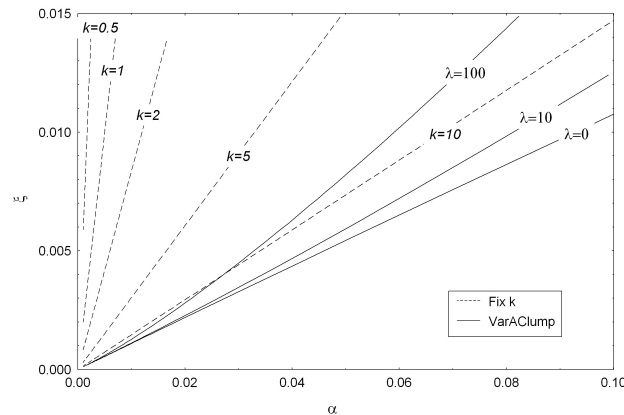**FIG. 6**. Stability regions (below the lines) for (Fix k) and (VarAClump) in the case $\delta = \infty$ and $\xi > 0$. The other parameters are $b=0.6$, $d=0.5$, $\nu=8.3e\text{-}04$, $h=100$, $\psi=0.5$, $\sigma=4$, $c=500$.

As can be seen from Figs. 6 and 7, the parameter region where the endemic equilibrium is stable is much smaller under (VarAClump) than under (Fix k). Since the results of

simulations of (Inf) appear to be very similar to those of (VarAClump) (Figs. 1 and 2), we believe that the same holds for stability boundaries. Thus, it seems that (Fix k) vastly underestimates, relatively to the other models, the region of parameters in which the endemic equilibrium is unstable, and sustained oscillations occur.
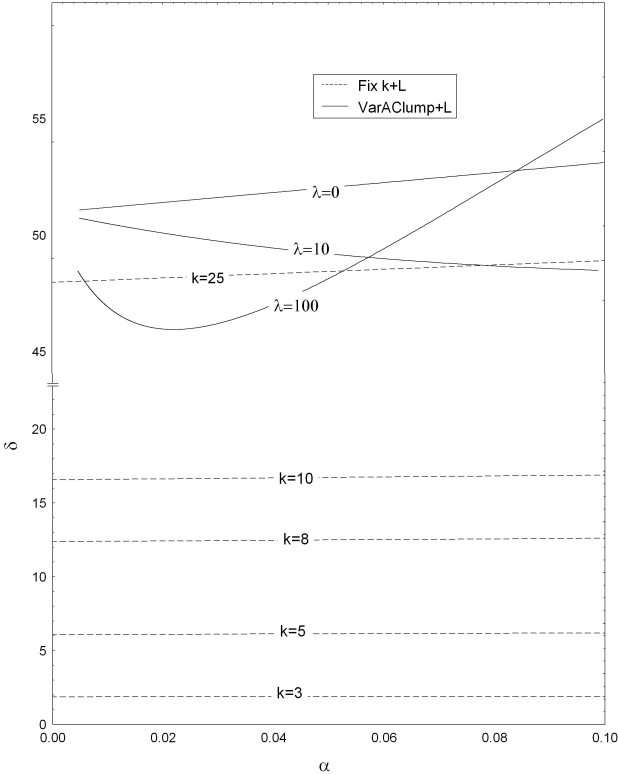
FIG. 7. Stability regions (above the lines) for (Fix k) and (VarAClump) model in the case $\delta < \infty$ and $\xi = 0$. The other parameters are $b=0.6$, $d=0.5$, $v=8.3\text{e-}04$, $h=100$, $\psi=0.5$, $\sigma=4$, $\beta=0.12$.

2.4 Features of cycles

When the endemic equilibrium is unstable, we found in all the simulations that the solutions tended to a limit cycle. It is important to know how the period of oscillations depends on models and parameter values, since it is often possible to estimate cycle length from empirical data.

It is however generally rather difficult to obtain analytic expressions for the period, as soon as a model becomes minimally complex. We found that model (Fix A+L) is rather

convenient in this respect; in fact, in that model, under the assumption of $\alpha=0$ and no carrying capacity, the equilibrium is always unstable; furthermore, it is possible to obtain asymptotic estimates for the imaginary part of the (unstable) eigenvalues of the equilibrium, and hence for the period of oscillations *(T)*, as the death rate of larvae gets either very small or very large.

When δ goes to 0 (i.e., the expected length of the free-living stage goes to infinity), the period goes to infinity as $\delta^{-1/2}$, according to the following formula

$$T \approx 2\pi \sqrt{\frac{(\sigma+d)-d\log(b/d)}{\delta d(\sigma+d)\log(b/d)}}, \tag{3}$$

on the other hand, when δ goes to ∞ (i.e., the expected length of the free-living stage goes to zero), the period tends to the constant value:

$$T \approx 2\pi \sqrt{1 / \left[(d\log(b/d)\left(\frac{(h\psi-\sigma-d)(\sigma+d)}{h\psi} - \frac{d\log(b/d)}{4} \right) \right]}. \tag{4}$$

The question arises of whether these explicit estimates, found under limiting conditions, for a simplified system, are useful in other contexts. First, it can be seen from Fig. 8 that these two estimates taken together fit well the exact local period in the (VarAClump+L) model over most of the range of δ.

Moreover, these estimates are rather good also when $\alpha>0$ and there is a finite carrying capacity (Fig. 9). To summarize, estimates (3) and (4) seem to work very well for model (VarAClump+L) for most reasonable parameter values, even though they were obtained from model (FixA+L) under limiting conditions.
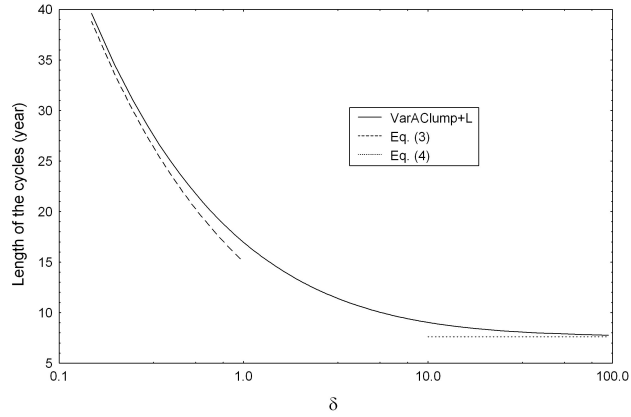
FIG. 8. Length of local period of oscillation for (VarAClump+L) compared with the asymptotic estimates for $\delta \to 0$ and $\delta \to \infty$ in the case $\alpha = 0$ and $N_K = +\infty$. The other parameters are $b=0.87$, $d=0.6$, $\sigma=4$, $A^*=20$, $\beta=7.7\ 10^{-6}$, $h=2\ 10^5$, $\psi=1$, $\xi=0.013$.

Moreover, it can be seen that the period is mainly influenced by the host and parasite demographic parameters b, d, δ and σ and, if δ is large, by h. On the other hand, the parameters that describe the impact of parameters on hosts, α and ξ, as well as λ, have a negligible effect on period length.
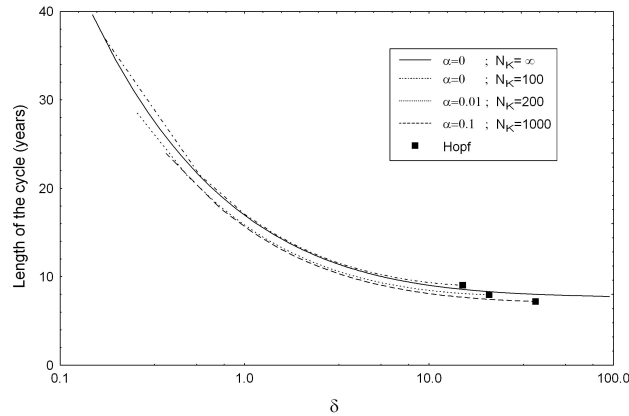
FIG. 9. Length of local period of oscillation for (VarAClump+L) in the cases $\alpha > 0$ and $N_K < +\infty$. The other parameters are the same of those in Fig. 8. Sustained oscillations occur for values of δ less than the Hopf point.

The final question concerns whether our estimates of the period, obtained as stated above through a linear analysis around the equilibrium, approximate well the true period of oscillations, that may fluctuate quite far from the equilibrium. To investigate this question,

we simulated the model (VarAClump+L) for several values of the parameters that yielded sustained oscillations. For each of those we computed the 'local' period (those obtained from linear analysis) and compared it with the 'global' period (that resulting from simulations). It can be seen (Fig. 10) that the two periods agree when δ is close to the value of δ at which Hopf bifurcation occurs (as analytically expected, since at that point the periodic solution merges into the equilibrium), but diverge rather strongly as δ moves away from the bifurcation point. In all the simulations, we found that the 'global' period is longer than the 'local' period; it would be interesting to know whether this is a general rule.

2.5 Density-dependence in parasites: model and results

Detecting density-dependence in the demographic parameters of parasites is very difficult, as argued in Hudson and Dobson (1997). On the other hand, it is plausible that even a slight dependence may affect deeply the dynamics of the system. Hence, it seems appropriate considering these effects in theoretical models.

The simplest rule for parasite mortality is to assume that it increases linearly with the number of parasites in the same host. Smith and Grenfell (1985) and Coyne and Smith (1994) present some data that seem consistent with such an assumption, although probably their data are better interpreted as resulting from immunological interactions.

Hudson and Dobson (1997) present data on the dependence of parasite fecundity on parasite density that seem to suggest a power law. Based on this assumption, they also presented an equation at the population level, whose derivation is however unclear. Only for the sake of mathematical tractability, we chose instead an exponential law, similar to that used for host fecundity, for the dependence of parasite fertility on the number of

parasites in the same host. From these rules (Tab. 1), and the negative binomial assumption, we obtained the following equations:

$$\begin{cases} \dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - \nu N - \alpha x) \\[2mm] \dfrac{dx}{dt} = x(-\sigma - \sigma_B(A+x) - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) + \beta\psi L \\[2mm] \dfrac{dA}{dt} = -(A-1)(\sigma + \sigma_B(3A+x) + \alpha A + \dfrac{\beta\psi L}{x}) + x(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - 2\sigma_B A) + \dfrac{\beta\psi L}{x}\lambda \\[2mm] \dfrac{dL}{dt} = h(1-r)Nx[1+(A-1)r]^{-\frac{x}{A-1}-1} - \delta L - \beta LN. \end{cases}$$ (DensDepPar)

Notice that assuming an exponential law for the fecundity of an individual parasite implies that the function relating number of parasites in a host to total egg production (what is generally measured as EPG) has a humped shape, although the hump may be at a very large parasite number, if the density-dependent fertility reduction is weak.
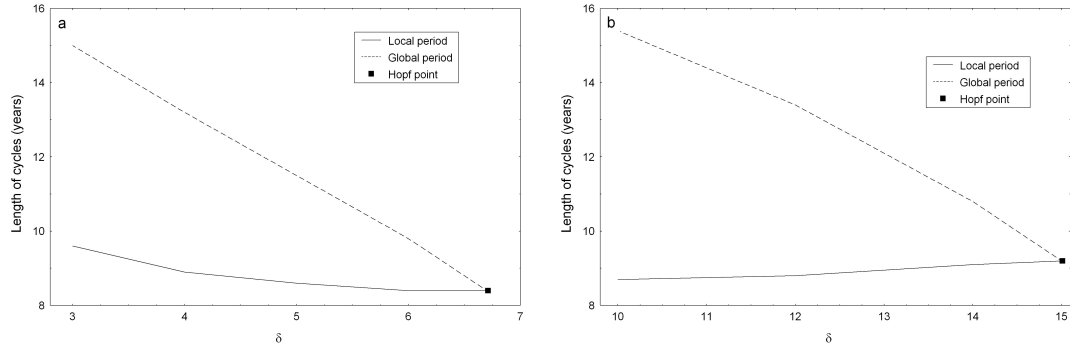
FIG. 10.Comparison between local and global length of the cycle in the case $\sigma = 4$ (a) and in the case $\sigma = 8$ (b). The other parameters are the same of those in Fig. 8 with $N_K=100$. Sustained oscillations occur for values of δ less than the Hopf point.

The effect of density-dependence in parasite fecundity and mortality on the stability of the endemic equilibrium is illustrated in Fig. 11, again through Hopf bifurcation diagrams. We chose values of the other parameters such as to yield sustained oscillations, without hosts' density-dependence. Then we show how the maximum value of hosts' carrying capacity, N_K, for which the endemic equilibrium is stable, increases with increasing r and σ_B.

FIG. 11. Stability regions (below the lines) for (DensDepPar) in the (N_K, r) and (N_K, σ_B) plane. The other parameters are b=1.8, d=1.05, ν=7e-03, α=3e-04, h=11, ψ=1, σ=1, β=0.1, ξ=2.78e-04, δ=10, λ=25.

In order to give the reader a better feeling for the figures, we try to give an empirical idea of the parameter values used in Fig. 11: in part a) at the right end of the abscissae axis (where the maximum value of N_K for equilibrium stability has increas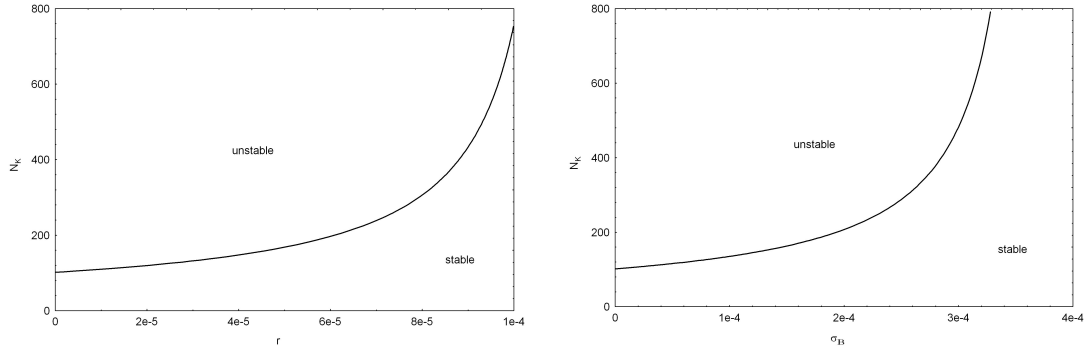ed more than 5 times with respect to the reference value) is r=1 10^{-4}; with this value, parasites in a host harbouring 3000 other parasites (around one standard deviation from the mean parasite burden with these parameter values) would have their fertility reduced about 25% relatively to optimal conditions; in part b) the right end of the abscissae axis corresponds to assuming that parasites in a host harbouring 3000 other parasites have doubled their mortality relatively to optimal conditions. It appears then that even a weak density-dependence in the parasite demographic parameters is a strongly stabilizing process for the system.

2.6 Discussion

We have reviewed here the results from several different models for host-macroparasite interactions. It seems worth summarizing their similarities and differences. The deterministic models examined differ in two respects: they differ in whether there is a fixed aggregation parameter in the model, or an aggregation mechanism (multiple

infections, or innate heterogeneities in susceptibility to infection), or neither one; second, they may be an exact translation of some mechanistic assumptions (the infinite model) or they may be based on some kind of mathematical approximation, generally the negative binomial assumption.

The first result obtained is that the negative binomial assumption works extraordinary well: simulations of the exact infinite models and of the approximating models are indistinguishable (Figs. 1 and 2), whether there exists some aggregating mechanism or not. Even the (Fix k) model that both is an approximation, and does not have an explicit aggregation mechanism, is not far from the infinite model, although the qualitative behaviour may be different. It must be remarked that we could not make a similar comparison for the model with host heterogeneity, since we did not consider any approximation of it. Instead, we studied how a simpler model (in which either a fixed aggregation parameter, or the average number of larvae per clump is estimated from data) would behave in such a situation. We saw that the simpler model captures some properties of the dynamics, although the qualitative behaviour may be different.

The second result is that the mechanism producing aggregation in parasite distributions has a strong influence on the stability of the system. As well known, there exists a tension in host-macroparasite models between stabilizing and destabilizing factors: when the former prevail, at least one equilibrium is stable, and the system will settle to one of those; on the other hand, when destabilizing factors prevail, sustained oscillations will occur. An important outcome of this comparison is that the stabilizing and destabilizing factors are the same in all models; hence, qualitative comparisons are robust to the choice of the model.

Anderson and May (1978) found that parasite aggregation is a very stabilizing factor. In a sense, we confirm this finding; however, we found that the aggregation

produced through our model of host heterogeneity stabilizes the system much more than that obtained through multiple infections. It turns out that the model with fixed aggregation, (Fix k), vastly underestimates the parameter region where oscillations occur if the correct mechanism is multiple infections (Figs. 6 and 7), while it underestimates the stability region if the correct model is the one with host heterogeneity (Figs. 4 and 5).

Note, however, that our model for host heterogeneity is very simplistic; possibly, in a model where immunity is acquired (and lost) dynamically (Grenfell *et al.*, 1995) the equilibrium stability would be less likely.

Note, finally, that just a slight density-dependence in parasite fecundity and/or mortality is another strongly stabilizing factor, and can turn the balance towards equilibrium stability (Fig. 11).

Third, we found a difference, mainly conceptual, between (Fix k) model and the models where aggregation is dynamical. In fact, in (Fix k) a large parasite aggregation (small k) makes it more difficult for parasites to regulate hosts, but does not influence its threshold for establishment (Tabs. 2 and 3). On the other hand, in (VarAClump) a large value of λ (mean number of larvae per infecting parcel) makes more difficult for parasites both to regulate hosts, and to get established into a population at carrying capacity. This fact has an intuitive explanation: for fixed values of all the other parameters, a large aggregation causes many hosts to escape from infection; hence, these hosts may be enough to let the population go on growing. Analogously, when we consider parasite establishment, a large aggregation would cause most parasites to occur in the same hosts; hence, even when parasites are extremely rare, they would suffer from increased host mortality due to other parasites; it is then expectable that the threshold for establishment increases with the level of aggregation. In our view, the lack of influence of k on R_0 in (Fix k) is a weakness of the model, or an implicit assumption: aggregating mechanisms are

such that they do not have any effect when parasites are very rare. Unfortunately, we do not have exact formulae for (InfClump) model, so that we cannot see the effect of λ in the infinite model, and we must rely on the approximate (VarAClump) model.

Cycles are one of the features that have always fascinated ecologists. Host-macroparasite interactions have already been shown (Anderson and May, 1978) to be one of their possible causes. As remarked above, the models with multiple infections make cycles more likely than what is expected from (Fix k), while the model with heterogeneity in susceptibility makes them less likely. Often, the approximate length of cycles is the feature most easily obtained from empirical data (whether they are census data, or shooting bags); hence, it may be useful that models yield explicit formulae for the length of cycles, so that mathematical predictions can be compared to actual data.

Although exact formulae for cycle length can rarely be obtained in nonlinear systems, we found that approximate formulae can be found for the models of interest; they actually represent or approximate the length of cycles («local cycle length») of the linear approximations performed at the equilibria of the nonlinear systems. We have shown (Figs. 8 and 9) that the approximations are rather robust to the exact system under study. Such approximations work, of course, well when the equilibrium of the nonlinear system is stable, which may be important since, in that case, stochastic simulations may be approximately cyclic with a similar period (Rosà *et al.*, 2003). On the other hand, when the equilibrium of the nonlinear system is unstable, the approximation of the period may not be so good when the cycle gets very far from the equilibrium (Fig. 10). In our simulations, we found that the true period of the nonlinear system («global cycle length») is always longer than the «local cycle length», but we do not know how general is the phenomenon. Finally, we remark that the model (InfHet+L) with heterogeneity in susceptibility to infection is rather simplistic, since it is assumed that individual hosts are born with a given

susceptibility, and keep that forever. More realistically, susceptibility to infection decreases with acquired immunity, and more complex models (Grenfell *et al.*, 1995; Chan and Isham, 1998) are needed to understand better the effect of acquired immunity on the dynamics of host-parasite interactions.

2.7 Appendix

List of models used

The infinite system with multiple infections

$$
\begin{cases}
\dfrac{dp_0(t)}{dt} = -(d + \nu \sum\limits_{i=0}^{\infty} p_i(t))p_0(t) - \dfrac{\beta}{\gamma} L(t)\psi p_0(t) + \sigma p_1(t) + b\sum\limits_{i=0}^{\infty} p_i(t)(1-\xi)^i \\[4mm]
\dfrac{dp_i(t)}{dt} = -(d + \nu \sum\limits_{i=0}^{\infty} p_i(t))p_i(t) - \alpha i p_i(t) - \sigma i p_i(t) - \dfrac{\beta}{\gamma} L(t)\psi p_i(t) + \sigma(i+1)p_{i+1}(t) \\[4mm]
\qquad\qquad + \dfrac{\beta}{\gamma} L(t)\psi \sum\limits_{l=1}^{i} \dfrac{\lambda^l}{l!} \dfrac{e^{-\lambda}}{1 - e^{-\lambda}} p_{i-l}(t) \qquad i \geq 1 \\[4mm]
\dfrac{dL(t)}{dt} = h\sum\limits_{i=0}^{\infty} i p_i(t) - \delta L(t) - \beta L(t)\sum\limits_{i=0}^{\infty} p_i(t)
\end{cases}
\qquad \text{(InfClump+L)}
$$

where $\gamma = \lambda/(1-e^{-\lambda})$.

The infinite system with host heterogeneity

$$
\begin{cases}
\dfrac{dp_{0,j}(t)}{dt} = -(d + \nu \sum\limits_{j=1}^{2}\sum\limits_{i=0}^{\infty} p_{i,j}(t))p_{0,j}(t) - \beta \psi_j L(t) p_{0,j}(t) + \sigma p_{1,j}(t) + q_j b\sum\limits_{j=1}^{2}\sum\limits_{i=0}^{\infty} p_{i,j}(t)(1-\xi)^i \quad j=1,2 \\[4mm]
\dfrac{dp_{i,j}(t)}{dt} = -(d + \nu \sum\limits_{j=1}^{2}\sum\limits_{i=0}^{\infty} p_{i,j}(t))p_{i,j}(t) - \alpha i p_{i,j}(t) - \sigma i p_{i,j}(t) - \beta \psi_j L(t) p_{i,j}(t) + \sigma(i+1)p_{i+1,j}(t) + \\[4mm]
\qquad\qquad + \beta \psi_j L(t) p_{i-1,j}(t) \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad j=1,2 \ ; \ \ i \geq 1 \\[4mm]
\dfrac{dL(t)}{dt} = h\sum\limits_{j=1}^{2}\sum\limits_{i=0}^{\infty} i p_{i,j}(t) - \delta L(t) - \beta L\sum\limits_{j=1}^{2}\sum\limits_{i=0}^{\infty} p_{i,j}(t).
\end{cases}
\qquad \text{(InfHet+L)}
$$

Approximate model with variable aggregation

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - \nu N - \alpha x) \\[4mm]
\dfrac{dx}{dt} = x(-\sigma + \dfrac{h\psi N}{c+N} - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) \\[4mm]
\dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{h\psi N}{c+N}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}}.
\end{cases}
\qquad \text{(VarA)}
$$

Approximate model with variable aggregation and multiple infection

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - vN - \alpha x) \\[2ex]
\dfrac{dx}{dt} = x(-\sigma + \dfrac{h\psi N}{c+N} - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) \\[2ex]
\dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{h\psi N}{c+N}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}} + \dfrac{h\psi N}{c+N}\lambda.
\end{cases}
\tag{VarAClump}
$$

Approximate model with fixed aggregation

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A*-1)\xi]^{-\frac{x}{A*-1}} - d - vN - \alpha x) \\[2ex]
\dfrac{dx}{dt} = x(-\sigma - \alpha A* - b[1+(A*-1)\xi]^{-\frac{x}{A*-1}}) + \beta\psi L \\[2ex]
\dfrac{dL}{dt} = hNx - \delta L - \beta LN.
\end{cases}
\tag{FixA+L}
$$

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Individual-Based vs. Deterministic Models for Macroparasites:

Host Cycles and Extinction

by

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3.0 Abstract

Our understanding of the qualitative dynamics of host-macroparasite systems is mainly based on deterministic models. We study here an individual-based stochastic model that incorporates the same assumptions as the classical deterministic model. Stochastic simulations, using parameter values based on some case studies, preserve many features of the deterministic model, like the average value of the variables and the approximate length of the cycles.

An important difference is that, even when deterministic models yield damped oscillations, stochastic simulations yield apparently sustained oscillations. The amplitude of such oscillations may be so large to threaten parasites' persistence.

With density-dependence in parasite demographic traits, persistence increases somewhat. Allowing instead for infections from an external parasite reservoir, we found that host extinction may easily occur. However, the extinction probability is almost independent of the level of external infection over a wide intermediate parameter region.

3.1 Introduction

Our understanding of the qualitative dynamics of host-macroparasite systems is mainly based on deterministic models, starting from Anderson and May (1978) to the following developments (Rosà and Pugliese, 2002). From the deterministic models it is possible to obtain analytical results, which have been widely used in applications (Grenfell and Dobson, 1995; Hudson *et al.*, 2002), about the basic reproduction ratio of parasites (R_0), the conditions for host regulation, or for the stability of the equilibria of the system.

Recently, with the development of high-speed computers, individual-based simulation models are becoming increasingly popular; some recent examples related to host-parasite interactions include Wilber and Shapiro (1997), Peters and Lively (1999).

In simulation models, one can easily introduce many important factors missing from simple deterministic models, such as spatial structure with local interactions (Hess, 1996; Keeling, 1999), genetical and behavioural differences among individual hosts. If the rules of simulation models are very complex, it becomes however difficult to disentangle the effect of the different factors, and to reach the qualitative understanding yielded by deterministic models (Anderson and May, 1978).

In the present paper we restrict our considerations to simulation models that may be considered the stochastic counterpart of the deterministic models considered in Rosà and Pugliese (2002). The stochasticity present in the simulations is that intrinsic to the discrete nature of populations, what is often called "demographic stochasticity" (May, 1973). From the results of the simulations it is possible to judge how well the predictions of the deterministic models hold for simulation models and to understand the phenomena brought in by "demographic stochasticity" *per se*.

This analysis should give us some clues on what can be inferred about real host-parasite interactions (that will undoubtedly be more complex than our simulation models) from deterministic models. Moreover, these results can be the reference against which to study models that include other factors deemed to be important in the dynamics of host-parasite interactions.

3.2 Models

3.2.1 Individual-based stochastic model

In our individual-based stochastic model, each individual host is distinguished only by the number of parasites it harbours. Thus, at each time, the state of the system is determined by the infinite vector $n(t)=\{n_0(t),n_1(t),\ldots,n_i(t),\ldots\}$, where $n_i(t)$ is the number of hosts with i parasites. The total population for hosts and parasites are respectively:

$N(t)=\Sigma_i n_i(t)$ and $P(t)=\Sigma_i i n_i(t)$ (note that, with probability 1, there will always be only a finite number of hosts, so that the sums defining $N(t)$ and $P(t)$ are always finite). Mathematically, $n(t)$ is a Markov process with values in the state space $S=N^N$ while the parameter t (time) lies in the parameter space $T=(0,+\infty)$ (see Barbour and Kafetzaki,1993, for the rigorous definition of a similar model).

The biological processes we included in the model are hosts' births and deaths, parasite deaths, and new infections; the transition probabilities for each of these events follow the laws used in the deterministic models described in Rosà and Pugliese (2002).

Namely, we assume that hosts with i parasites have a birth rate of $b(1-\xi)^i$ (i.e., parasites decrease hosts' fertilities) and a death rate of $d(N)+\alpha i$ (parasites increase hosts' mortalities), while death rate of adult parasites is σ (density-independent, but see Section 4). The death rate $d(N)$ is assumed to be density-dependent, so that there exists a deterministic equilibrium N_K for the host population in absence of parasites. Here, we always used $d(N) = d_0 + (b- d_0)N/ N_K$ with $b > d_0$.

These assumptions can be translated in the rules for the transition probabilities, listed in Tab. 1. In fact, it is assumed that the probability that a host carrying i parasites gives birth to a new host within the time interval $(t, t+\Delta t)$ is equal to $b(1-\xi)^i \Delta t$ plus higher order terms in Δt. Summing over all hosts in the population, we obtain that the probability (conditional on the state $n(t)$ of the population) that a new host is born in the time interval $(t, t+\Delta t)$ is equal to

$\Sigma_i b(1-\xi)^i n_i(t)\Delta t + h.o.t.$

In this case, since hosts are assumed to be born parasite-free, the population state will move from $(n_0,n_1,\ldots,n_i,\ldots)$ to $(n_0+1,n_1,\ldots,n_i,\ldots)$. This is reported in Tab. 1 as $P(n(t+\Delta t)-n(t)= e_0 \mid n(t))$ where e_0 is the vector $(1,0,0,\ldots)$.

Analogously, the probability (conditional on the state $n(t)$) that in the time interval $(t, t+\Delta t)$ the death occurs of a host carrying i parasites is equal to $(d(N)+\alpha i)n_i\Delta t + h.o.t.$ In this case, the population state will move from $(n_0,n_1,\ldots,n_i,\ldots)$ to $(n_0,n_1,\ldots,n_i\text{-}1,\ldots)$, i.e. $n(t+\Delta t)=n(t)-e_i$, as reported in Tab. 1.

TABLE 1. Transition probabilities regarding the four processes considered in the individual-based model.

Parasite's death	$P(n(t+\Delta t)-n(t)=e_{i-1}-e_i \mid n(t))=\sigma n_i(t)\Delta t+o(\Delta t)$, $i=1,\ldots$ where $e_i=(\ldots,0,1,0,\ldots)$
New infection	$P(n(t+\Delta t)-n(t)=e_{i+l}-e_i \mid n(t))=\dfrac{h\psi\,q_l P(t)}{c+N(t)}\,n_i(t)\Delta t+o(\Delta t)$, $i=0,\ldots$; $l=1,\ldots$
	with $q_l=\dfrac{\lambda^l}{l!}\dfrac{e^{-\lambda}}{1-e^{-\lambda}}$
Host's death	$P(n(t+\Delta t)-n(t)= -e_i \mid n(t))=(d+[(b-d)/N_K]N+\alpha i)\,n_i(t)\Delta t + o(\Delta t)$, $i=0,\ldots$
Host's birth	$P(n(t+\Delta t)-n(t)= e_0 \mid n(t))=\Sigma_i b(1-\xi)^i\,n_i(t)\Delta t + o(\Delta t)$, $i=0,\ldots$

Again, the probability (conditional on the state $n(t)$) that in the time interval $(t,t+\Delta t)$ the death occurs of a parasite in a host carrying i parasites is equal to $\sigma i n_i\,\Delta t + h.o.t.$ In this case, the population state will move from $(n_0,n_1,\ldots,n_{i-1},n_i,\ldots)$ to $(n_0,n_1,\ldots,n_{i-1}+1,n_i-1,\ldots)$, i.e. $n(t+\Delta t)=n(t)+ e_{i-1} - e_i$, as reported in Tab. 1.

Infections are slightly more complex to describe. The infection rate is expressed in terms of N and P, and is equal to $h\psi P/(c+N)$. This form is justified on the basis of a submodel that considers the indirect transmission of parasite through free-living stages (Anderson and May, 1978). Simple assumptions on their dynamics and a time-scale argument (lifespan of free-living stages being much shorter than that of adult parasite inside a host) lead to this form, where h is the rate at which infecting stages are produced by adult parasites, ψ is the probability that ingested infecting stages develop into adult parasite, and $c=\delta/\beta$ with β the encounter rate between hosts and infecting stages, and δ the

death rate of infecting stages. We refrained from explicitly including infecting stages in the simulations, to keep the computation time within reasonable bounds. In this case, it can be noticed that, in the simulations, we do not actually need the two parameters h and ψ, but only the lumped parameter $h\psi$. Finally, it is assumed that, in any infection, a host ingests a random (according to a truncated Poisson law of parameter λ) number of free-living stages. These assumptions imply that the probability (conditional on the state $n(t)$) that in the time interval $(t, t+\Delta t)$ a new infection occurs in a host carrying i parasites is equal to

$$\frac{h\psi P}{c+N} n_i \, \Delta t \; + h.o.t.$$

In this case, the host will ingest l larvae with probability q_l given in Tab. 1. Hence, the population state will move from $(n_0, n_1, \ldots, n_i, \ldots)$ to $(n_0, n_1, \ldots, n_i\text{-}1, \ldots, n_{i+l}+1, \ldots)$ with

probability $\dfrac{h\psi q_l P}{c+N} n_i \, \Delta t \; + h.o.t$ as reported in Tab 1.

We investigated the model only through simulations. At any moment in time there will be a finite number of hosts, each with a finite number of parasites. The four biological processes considered occur asynchronously (Durrett and Levin, 1994); this means that, given the state of the system at time t, the waiting time for the next event is exponential with a rate given by the sum of the rates of every event. For instance, the probability that a host carrying i parasites dies in the interval $(t, t+\Delta t)$ is equal to $(d+\alpha i)\, n_i(t)\Delta t + o(\Delta t)$; in other words, if no other events occur before, the waiting time for the next death of a host carrying i parasites is an exponential variable of parameter $n_i(t)(d+\alpha i)$. Summing over all possible events, we find that the waiting time for the next event is an exponential variable with parameter equal to the sum of the rates of each event. In the simulations, by extracting pseudo-random numbers, we find the time and the type of next event, according to the distributions obtained from these rates. Then we update all the relevant variables and the process starts again in the same way, because of the Markov property.

The simulations stopped either when no parasites were left in the system, or when the final time (generally $t=100$) was reached.

[If useful, the code of the simulations can be made available on the Web at the Journal site].

3.2.2 Deterministic model and its approximation

As explained in the Introduction, we will study how the predictions of deterministic models apply to the stochastic model based on the same assumptions.

The deterministic counterpart of the individual-based model presented in the previous section is the infinite model:

$$
\begin{cases}
\dfrac{dp_0(t)}{dt} = -(d+\dfrac{(b-d)}{N_K}\sum_{i=0}^{\infty}p_i(t))p_0(t) - \dfrac{h\psi\sum_{i=1}^{\infty}ip_i(t)}{\gamma[c+\sum_{i=0}^{\infty}p_i(t)]}p_0(t) + \sigma\, p_1(t) + b\sum_{i=0}^{\infty}p_i(t)(1-\xi)^i \\[4ex]
\dfrac{dp_i(t)}{dt} = -(d+\dfrac{(b-d)}{N_K}\sum_{i=0}^{\infty}p_i(t))p_i(t) - \alpha ip_i(t) - \sigma ip_i(t) - \dfrac{h\psi\sum_{i=1}^{\infty}ip_i(t)}{\gamma[c+\sum_{i=0}^{\infty}p_i(t)]}p_i(t) + \sigma(i+1)p_{i+1}(t) + \\[4ex]
\qquad + \dfrac{h\psi\sum_{i=1}^{\infty}ip_i(t)}{\gamma[c+\sum_{i=0}^{\infty}p_i(t)]}\sum_{l=1}^{i}\dfrac{\lambda^l}{l!}\dfrac{e^{-\lambda}}{1-e^{-\lambda}}p_{i-l}(t) \qquad i\geq 1
\end{cases}
\qquad \text{(InfClump)}
$$

where $p_i(t)$ represent the number (assumed to be a continuous variable) of hosts carrying i parasites, and $N(t) = \sum_{i=0}^{\infty}p_i(t)$ is the total host population. Moreover, $\gamma=\lambda/(1-e^{-\lambda})$ and $d=d(N)$.

Indeed, system (InfClump) can probably be obtained through an appropriate limit of Markov processes $n(t)$. Precisely, if we have a sequence $n^j(t)$ of processes, as defined in the previous Section but whose carrying capacity N_K^j grows to infinity as $j\to\infty$, defining $p_i^j(t) = \dfrac{n_i^j(t)}{N_K^j}$, the law of large numbers, as used in Barbour and Kafetzaki (1993) or

Arrigoni and Pugliese (2001), should imply that $p_i^j(t)$ converge as $j \to \infty$, to the solution of

(InfClump) with $N_K = 1$.

As widely illustrated in Rosà and Pugliese (2002), the system (InfClump) is well

approximated by the following three-dimensional system:

$$\begin{cases} \dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - (b-d)N/N_K - \alpha x) \\[2mm] \dfrac{dx}{dt} = x(-\sigma + \dfrac{h\psi N}{c+N} - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) \\[2mm] \dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{h\psi N}{c+N}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}} + \dfrac{h\psi N}{c+N}\lambda, \end{cases} \qquad \text{(VarAClump)}$$

where N represents the host population size, x the mean parasite burden and A is the

measure of the aggregation of the parasite distribution defined as the ratio of the variance

to the mean of adult parasite burden.

System (VarAClump) is a variant of the classical model introduced by Anderson

and May (1978); in that model, an infinite system similar to (InfClump) is 'closed'

assuming that the parasite distribution is negative binomial with fixed aggregation

parameter k. It is not conceptually possible to build stochastic simulations with this

procedure, since k is a population parameter that cannot be translated into individual-based

processes. The parameter λ that regulates the number of ingested free-living stages per

infection event has an effect similar to that of k on the dynamics of the system (Rosà and

Pugliese, 2002), but has the advantage of corresponding to an individual biological

process. Other aggregating mechanisms could be built into the simulations, but here we

considered only the one depending one multiple infections, as measured by parameter λ.

It is well known, and widely shown in Rosà and Pugliese (2002) that the

destabilizing factor included in models for macroparasites are the parasite-induced

reduction of host fertility ($\xi > 0$), and low values of the free-living stages mortality (long

lifespan of free-living stages). If one allows for long-lived free-living stages, the explicit

differential equation for the free-living stages has to be introduced in the model, obtaining a system which has been studied in detail in Pugliese *et al.* (1998) and in Rosà and Pugliese (2002) under the name (VarAClump+L). As explained above, we did not consider explicitly free-living stages in the simulations because of the computational burden.

3.3 Results of stochastic simulations

We performed the stochastic simulations outlined above for three different sets of parameters. The first concerns the well known red grouse (*Lagopus lagopus scoticus*) - *Trichostrongylus tenuis* system in northern England (Dobson and Hudson, 1992), the second refers to the infection by Trichostrongylidae in a chamois (*Rupicapra rupicapra* L.) population in the Brenta mountain group (northern Italy) (Rosà *et al.*, 1997) and the third concerns the *Ascaridia compar* infection in rock partridge (*Alectoris graeca saxatilis*) in Trentino region (northern Italy) (Rizzoli *et al.*, 1997; Rizzoli *et al.*, 1999). The parameter values we used for our simulations are reported in Tab. 2. We let the simulations start from close to the deterministic equilibrium of each parameter set.

TABLE 2. Parameter values used in the stochastic simulations for the red grouse-T*richostrongylus tenuis*, the chamois-Trichostrongylidae and the rock partridge-*A. compar* systems.

Parameter	Red grouse Values	Chamois Values	Rock partridge Values	Units
b	1.8	0.44	1.8	year^{-1}
d	1.05	0.23	1.6	year^{-1}
N_K	107	1500	75	host
σ	1	1.08	4	year^{-1}
$h\psi$	11	20	2e+5	year^{-1}
c	100	8250	1.32e+6	host
α	3e-4	1.5e-4	0	worm^{-1} year^{-1}
ξ	2.78e-4	0	1.8e-2	worm^{-1} year^{-1}
λ	400	20	0	

In Fig. 1 we show two stochastic simulations for each of the parameter sets representing the red grouse and chamois systems (Tab. 2). The simulations are compared to the numerical solution of the deterministic model (VarAClump). In the case of red grouse, the deterministic model exhibit sustained oscillations, while the dynamics of the deterministic system with the chamois parameters is characterised by damped oscillations (in fact, in that case $\xi=0$).

It appears from Fig. 1 that in both cases the stochastic simulations exhibit fluctuations whose amplitude is not decreasing over the 100 year period; this is confirmed by the periodograms of the simulations, shown in Fig. 2, all of which present a well-defined peak. Indeed, it has already been shown in the literature (Bartlett, 1960; Nisbet and Gurney, 1982; Kaitala *et al.*, 1996) in several contexts that, when a deterministic model has damped oscillations, it may occur that a stochastic version of that model exhibits sustained oscillations.

We investigated the period and the average of these fluctuations. The spectral analysis (Fig. 2) of the stochastic simulations shown in Fig. 1 exhibits an apparent period consistent with what found in the deterministic period; in fact, the period of the oscillations in the deterministic model is close to 6.5 years for the red grouse parameters, and around 15 years for the chamois parameters.

This is further explored in Fig. 3, where the apparent period of oscillations and the temporal averages of some population statistics are shown for each of 20 stochastic simulations, together with the values at the deterministic equilibrium for the same quantities.
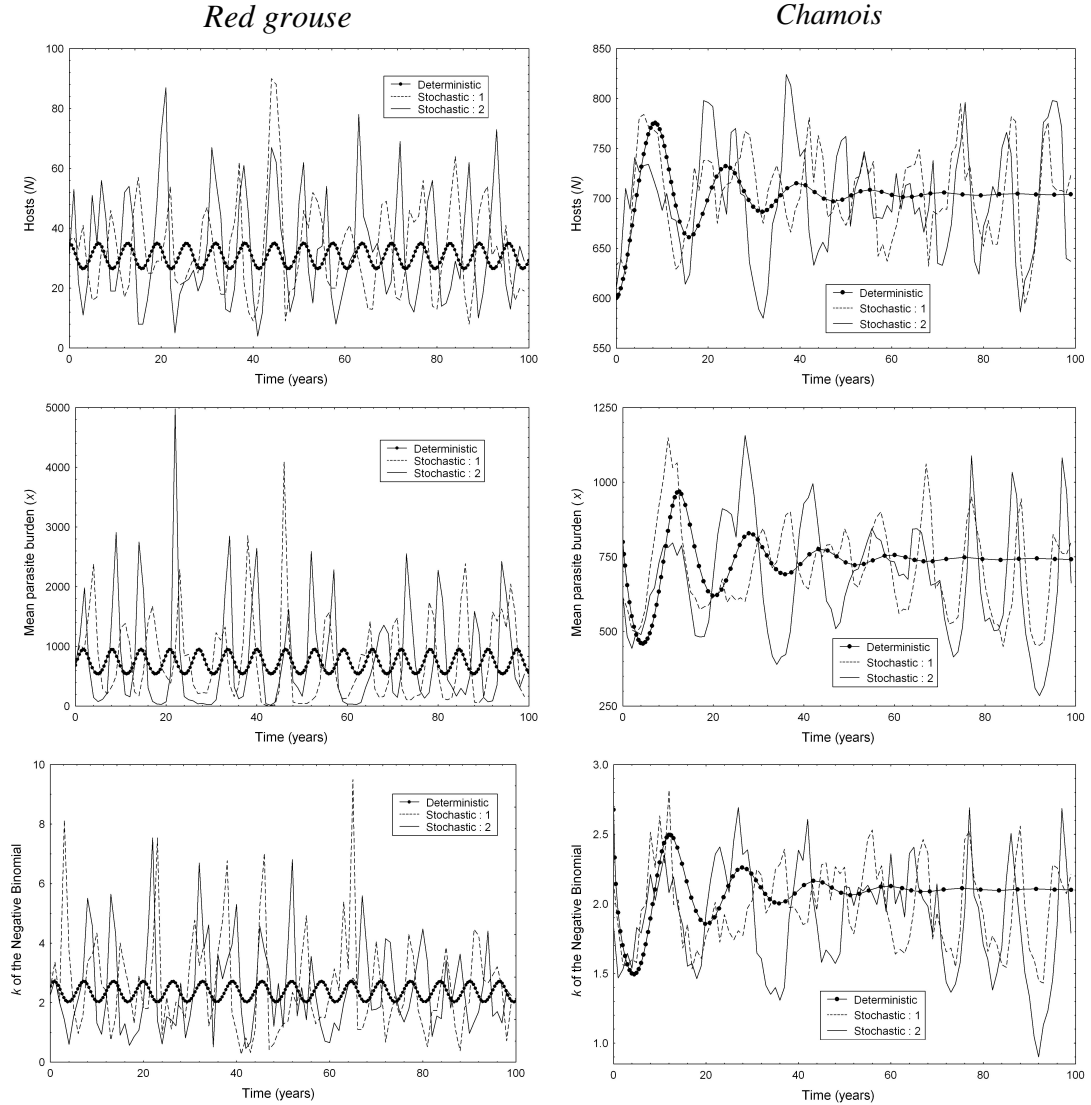
Red grouse — *Chamois*

FIG. 1. Deterministic model (VarAClump) and stochastic simulations for hosts (N), mean parasite burden (x) and k of the Negative Binomial distribution. The first column shows two simulations for the red grouse–*Trichostrongylus tenuis* system. The second column two simulations for the Trichostrongylidae-chamois system. Parameters are in Tab. 2.

We used the parameter set representing the red grouse system, but trying different values of h, parasite fertility. For each value of h we chose the first 20 simulations that reached the final time t=100. In Fig. 3 we show (closed triangles) the length of cycles (estimated as the maximum of the periodogram) and the temporal averages, over the last 20 years of the simulations, of the host number (N), of the mean parasite number (x), and of the aggregation parameter k of the Negative Binomial distribution ($k=x/(A-1)$); in the

same figure, we show the corresponding quantities for the deterministic model (line): value at equilibrium of N, x and k, and oscillation period estimated from the imaginary part of the largest eigenvalues at the equilibrium.
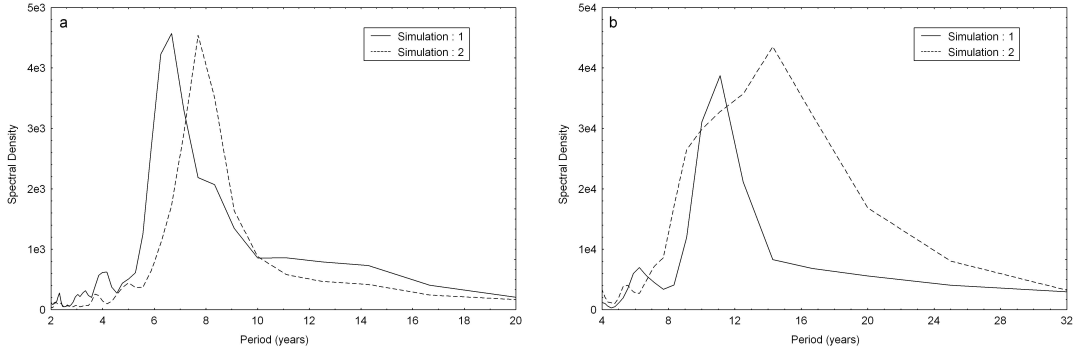

FIG. 2. Spectral analysis of host number (N) in the stochastic simulations of Fig.1: (a) red grouse–*Trichostrongylus tenuis* system; (b) Trichostrongylidae-chamois system.
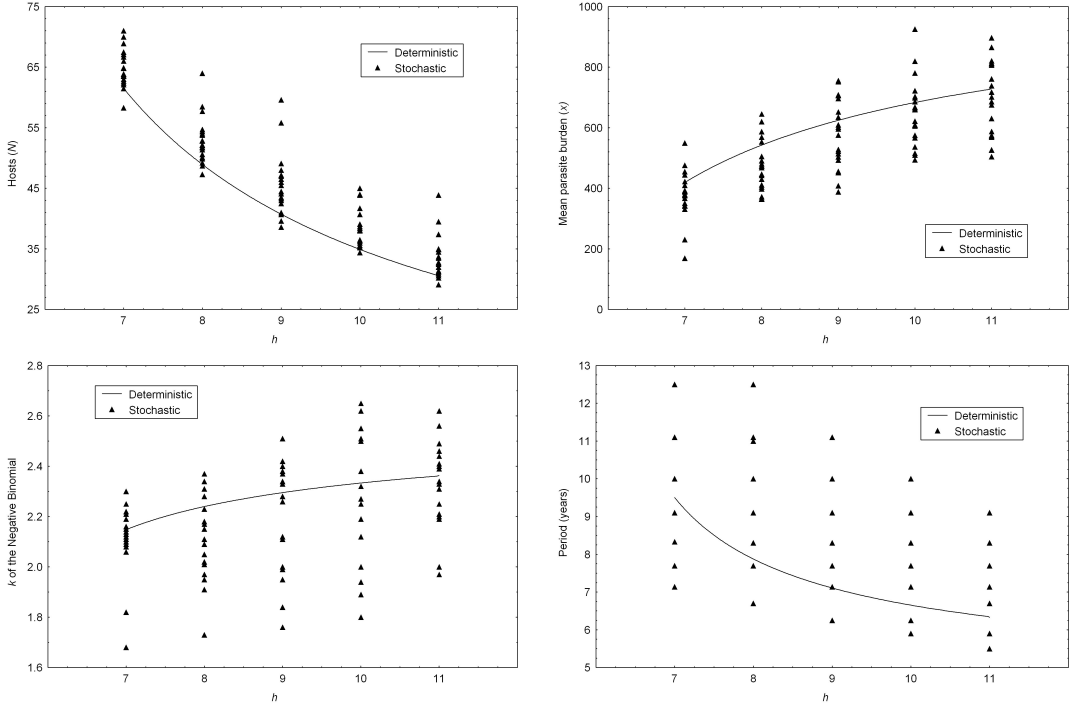
FIG. 3. Temporal averages (between $t=80$ and $t=100$) of hosts (N), mean parasite burden (x), the aggregation parameter k of the Negative Binomial distribution and the period of oscillation (T) for the deterministic solution (VarAClump), and 20 stochastic simulations using the red grouse–*Trichostrongylus tenuis* parameter of Tab. 2.

Although different simulations yield different results within a band of variation (because of the inherent stochasticity of the individual-based model), it can be seen that the

statistics of the stochastic simulations are close to the predictions from deterministic model; moreover, when h changes, deterministic and stochastic results follow the same trends.

In conclusion, it seems that the predictions (as for average values and period of fluctuations) of the deterministic model apply rather well to stochastic simulations.

We finally remark that all the simulations shown have a relatively high value of the parameter λ; the simulations (not shown) with $\lambda=0$ (infections occuring with only one parasite per time) have much larger and irregular fluctuations, especially for the variables A and k. It seems thus necessary to introduce some aggregation mechanism in the simulations in order to have a mild behaviour of these statistics.

An important feature of stochastic models, in contrast to deterministic ones, is the possibility of population extinction; in this case, one could have extinction of the only parasite population, or of both hosts and parasites.

Since in our model growth to infinity of the population is impossible (because of density-dependent host mortality), it is clear that extinction is certain, as in all regular birth-and-death processes (Karlin and Taylor, 1975). However, it is well known that the average time to extinction of a population grows exponentially with the carrying capacity of the population (Andersson and Djehiche, 1998), and can be astronomically long already for moderate values of the carrying capacity. We investigated the probability of extinction over a finite time interval by assessing how many times our simulations terminated before the final time. We generally chose *100* years as final time, because we think it is a relevant time scale, compared to the rate of habitat change.

For the parameter values of the chamois case study, no extinctions (of either parasites only, or of both hosts and parasites) occurred in 100 simulations (note that $N_K=1500$ and that also mean parasite burden is large). Using the parameter values for the

red grouse system, approximately 1% of the simulations (36 out of 3000) reached the final time $t=100$ without extinctions, while all simulations representing the rock partridge- *A. compar* system show extinction of the parasite population while hosts oscillate around the carrying capacity.

3.4 Density-dependence in parasite population

In the simulations presented in the previous Section, parasite extinction occurred always for the rock partridge system, and very often for the red grouse system, in contrast to the apparent persistence of these host-parasite association over a long period (Hudson and Dobson, 1992). It is intuitive, and will be further discussed below, that this problem could be solved increasing the carrying capacities; the ones we used are however based on field estimates. Concerning in particular the rock partridge, we used the maximum values of host density (7.5/km^2) found in Trentino (northern Italy) and the extent of suitable area for the rock partridge in a mountain group (typically around 10 km^2), obtaining a carrying capacity around 75 individuals. Hence, we conclude that some factors missing from the model must be responsible for this persistence.

Among the possible factors, in this Section we concentrate our attention on the density-dependence in parasite fertility and/or mortality (Paterson and Viney, 2002). In fact, as observed in the deterministic models (Rosà and Pugliese, 2002) just a slight density-dependence in the parasite is a strongly stabilizing process for the system; in other words, parasites cannot reach very high peaks in abundance and consequently drastic crashes in both host and parasite populations are avoided.

As in Rosà and Pugliese (2002), here we assume very simple rules for the density-dependence in parasite fertility and mortality. The parasite mortality increases linearly with the number of parasites present in the same host while we chose an exponential law for the

dependence of parasite fertility. More precisely, the mortality for parasites in hosts carrying i parasites is given by $\sigma+(i\text{-}1)\sigma_B$, while the fertility for parasites in hosts that harbour i parasites is equal to $h(1\text{-}r)^{i\text{-}1}$. Note that we used $i\text{-}1$ in the previous formulae so that a parasite alone in a host (when density-dependent factors should not operate) has the same fertility and mortality independently of the values of the parameters σ_B and r that measure density-dependence.
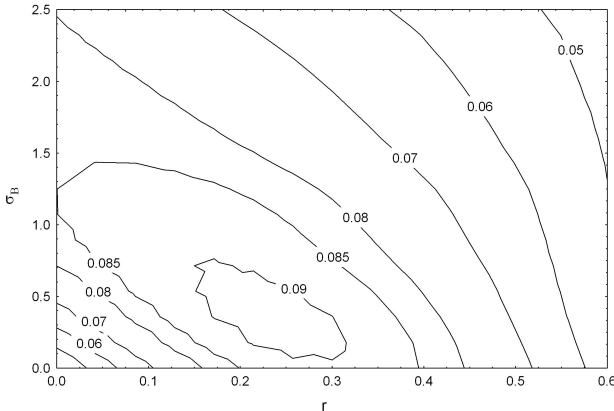
FIG. 4. Survival probability in 1000 simulations of 20 years for different values of the parameters concerning the density-dependence in parasites (σ_B and r). The other parameters are those of Tab. 2 regarding the *A.compar*-rock partridge system with $N_0=30$ and $x_0=4$.
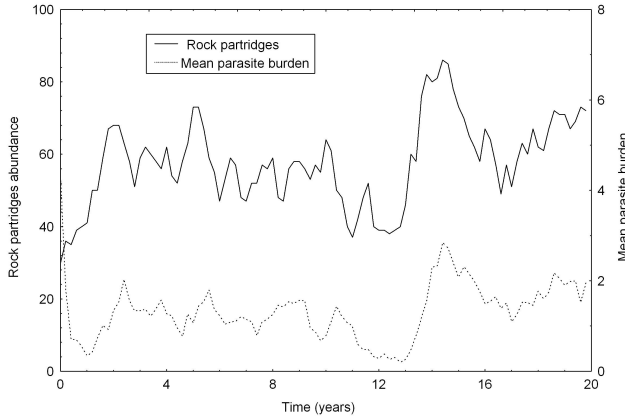
FIG. 5. Temporal dynamics for rock partridges and *A. compar* considering density-dependence in parasites. The values of $\sigma_B=0.5$ and $r=0.2$ are those where the survival probability in Fig. 4 is maximum. The other parameter values are those of Fig. 4.

The survival probability of parasites (over 20 years of simulations) is shown in Fig. 4 for different combination of σ_B (increase in parasite mortality) and r (reduction in

parasite fecundity) using the rock partridge parameter set. Here we used a time interval of 20 years, since very few simulations persisted longer for any combination of σ_B and r. Note however that we used $N_0 = 30$ as starting value for the simulations; using a higher value of N_0; we would obtain marginally higher survival probabilities.

Moving from the point without density-dependence ($\sigma_B=r=0$), where no simulations out of 1000 persisted 20 years, the persistence of parasites in the system increases for positive values of both σ_B and r till it reaches a maximum value (around 9%) for an intermediate region of these parameters (approximately when $0.15<r<0.32$ and $0.05<\sigma_B<0.75$). A further increase in the density-dependence affects too much the demographic parameters of parasites and as a result the survival probability of parasites in the system decrease (Fig. 4).

Looking at the temporal dynamics for host-parasite interaction, choosing σ_B and r in the region of maximum survival probability, the dynamic results quite stable and parasites cannot reach very high peaks (Fig. 5). This results is not surprising and reflects what we obtained in deterministic model (Rosà and Pugliese, 2002). Still, even choosing the best possible values for σ_B and r, only 2 simulations (out of 1000) reached $t=100$, and in both of them the parasites got extinct before $t=110$.

3.5 Stochastic simulations with external infection

Another possible factor that could be responsible for the persistence of parasites in the system is the presence of other species acting as a reservoir for the infection process; some empirical evidence for this factor in the case of the rock partridge population is presented in the Discussion. Here, we change the basic model by adding an additional input to the infection process due to the presence of another host species.

For the sake of simplicity, at this stage we did not model explicitly the two hosts population (by adding additional differential equations, as in Schmitz and Nudds (1994), or stochastic variables). Instead, we assumed that one of the host population was much larger than the other and supported the parasite at more or less constant level; hence, we modelled the dynamics of only the smaller host population (e.g., rock partridge), adding an additional constant term f (due to parasites emerging from the other host species) in the infection rate, which becomes now equal to $\psi(hP+f)/(c+N)$. In this formula, we also assumed that no infecting stages produced by adults in a rock partridge are picked up by hosts of the other species. The deterministic system we obtain is

$$
\begin{cases}
\dfrac{dN}{dt} = N(b[1+(A-1)\xi]^{-\frac{x}{A-1}} - d - (b-d)N/N_K - \alpha x) \\[2ex]
\dfrac{dx}{dt} = x(-\sigma + \dfrac{h\psi N}{c+N} - \alpha A - b[1+(A-1)\xi]^{-\frac{x}{A-1}}) + \dfrac{\psi f}{c+N} \\[2ex]
\dfrac{dA}{dt} = -(A-1)(\sigma + \alpha A + \dfrac{h\psi N}{c+N}) + bx[1+(A-1)\xi]^{-\frac{x}{A-1}} \\[2ex]
\qquad + \dfrac{h\psi N}{c+N}\lambda + (\lambda+1-A)\dfrac{\psi f}{(c+N)x}.
\end{cases}
\qquad \text{(VarAExtInf)}
$$

Obviously, with an external input, it is impossible that parasites get extinct; in fact, one can see from the second equation in (VarAExtInf) that $x(t)$ will always stay positive if $f > 0$. On the other hand, one can see that the host population will get extinct ($N(t)$ will tend to 0) if f is large enough. These results of the deterministic models are confirmed by the simulations: just a low value of external infection f is enough to allow *A. compar* to persist in the host population, while, when f is very large, the rock partridge population goes to extinction, because the mean parasite burden will be high and host fertility will become very low. We explored how the process of host persistence depends on the level of external infection.

Fig. 6 shows the probability of extinction (defined as the fraction of simulations where extinction occurred in a 100-year interval) of the rock partridge population for

different values of the external infection f, of the carrying capacity N_K and of the initial value N_0. The values chosen for N_K are 75 (the best estimate for a typical rock partridge population) and twice as much (what might have been more typical decades ago, before the numerical decline of the species); we tried N_0 equal to the carrying capacity, and to half of it (what may be typical in a population affected by parasites).
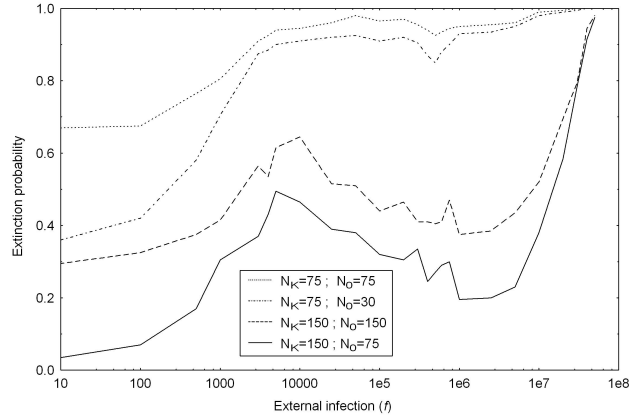
FIG. 6. Effect of the external infection (f) on the extinction probability of hosts in the stochastic model for different values of host carrying capacity (N_K) and for different levels of the initial population (N_0). The other parameters are those of Tab. 2 regarding the *A. compar-* rock partridge system.

As expected, the probability of extinction decreases as N_K is increased. Less expectedly, the probability of extinction increases as N_0 is increased, especially when the external infection f is low.

FIG. 7. Probability of extinction in 10 years for different levels of the initial population (N_0) without external infection. The parameters are those of Tab. 2 regarding the *A. compar-* rock partridge system but with N_K=150. The initial level of parasite infection is x_0=1.

To explore this fact, we studied (see Fig. 7) how, for a given initial level of parasite infection and no external infection afterwards, the probability of extinction in a short period (10 ye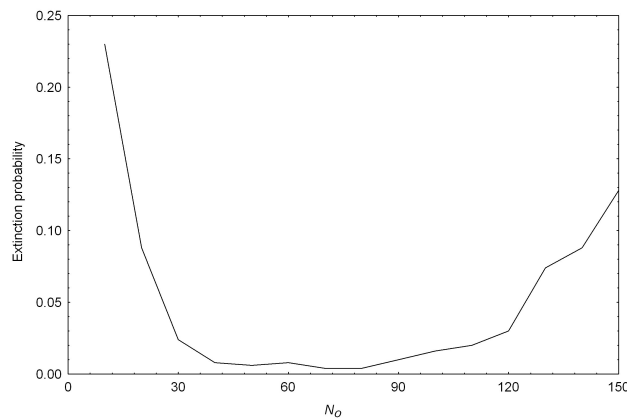ars) depends on the initial level of the population. It can be seen that, all other things being equal, the probability of extinction first declines to around 0 for populations initially between 40 and 90 individuals (against a carrying capacity of 150, chosen to better illustrate the pattern) and then increases again as the initial population grows closer to its carrying capacity.
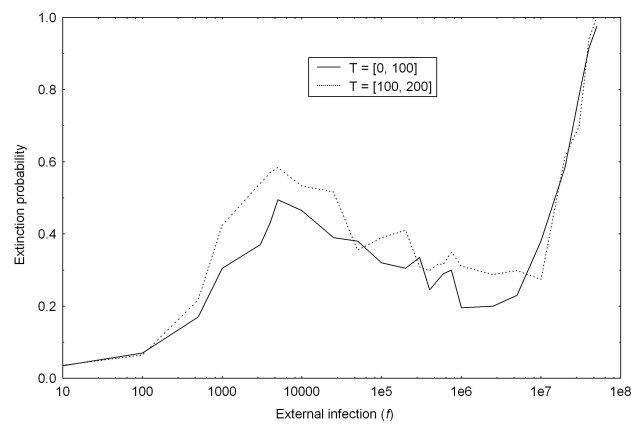
FIG. 8. Comparison between the effect of the external infection (f) on the probability of host extinction for the first 100 years of simulation with the following 100 years in the case with N_K=150 and N_0=75. The other parameters are those of Tab. 2 regarding the *A. compar*- rock partridge system.

Another interesting result that can be seen in Fig. 6 is how the extinction probability depends on the level of external infection f: as expected, when external infection is very high, host extinction is certain, while the probability of extinction declines to 0 as external infection goes to 0. However, the increase of the extinction probability with f is not monotonic: over a wide intermediate region (more or less when f is between 10^4 and 10^7 in our figure), host extinction probability is more or less independent of the level of external infections, and actually, for some values of the carrying capacity, even decreases with increasing f.

It may be wondered whether this pattern is due to transient effects. To avoid this, one may use as starting condition the quasi-equilibrium distribution of hosts and parasites, conditional to non-extinction. In order to approximate this, we let the simulations run for 200 years, and computed the extinction probability as the fraction of the simulations that did not reach 200 years but had reached 100 years over the simulations that had reached 100 years.
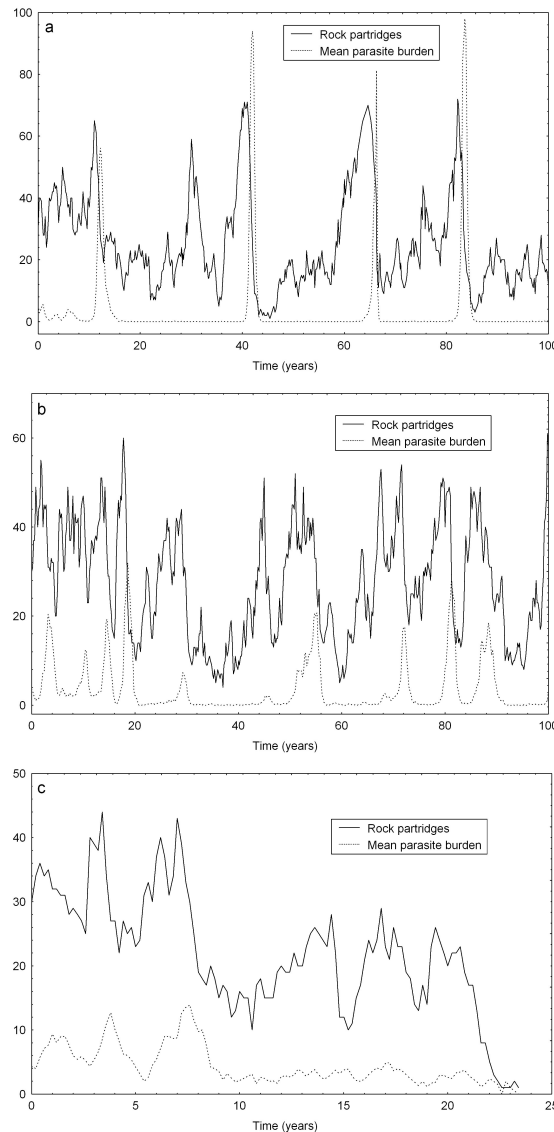

FIG. 9. Simulations of the stochastic model for increasing values of the external infection: (a) $f = 10^5$; (b) $f = 5 \cdot 10^5$; (c): $f = 10^7$. The other parameters are those of Tab. 2 regarding the *A. compar-* rock partridge system.

In fact, it is expected that at $t=100$ the distribution of the simulations that have reached such t will be close to quasi-equilibrium. It is shown in Fig. 8 that the extinction probability computed in this way is very similar, at least for $N_K=150$ and $N_0=75$, to that one observed in the first 100 years of simulation.

For different values of f, the visual pattern of the simulations changes, as shown in Fig. 9. When f is relatively low (not shown), the host population is almost always parasite-free; when an infection occurs, the host population is generally at a relatively large size, so that there is a violent crash that frequently results in host extinction. For larger values of f, infections are so frequent that host population does not have time to reach the carrying capacity in the parasite-free period (Fig. 9a). When f is further increased (Fig. 9b), parasites are almost always present at low levels, and the host population fluctuates rather erratically remaining generally far from zero and from the carrying capacity. In this parameter region, which is very narrow for $N_K = 75$ but wider for $N_K = 150$, extinction probability is lower than for smaller f. Finally, when f reaches a higher value, the average parasite burden becomes so high (Fig. 9c) that there is a deterministic decline of the host population.

3.6 Discussion

The first result arising from our stochastic simulations of host-macroparasite systems is that the results of deterministic models mainly hold when demographic stochasticity is added. In fact, as shown in Fig. 3, the average values (along an individual simulation) of host density, parasite burden and parasite aggregation are close to the value at the deterministic equilibrium, and show similar trends with respect to parameters.

One of the most interesting aspects of host-macroparasite interactions is the possibility of inducing population cycles (Anderson and May, 1978). Sustained oscillations

that look almost cyclic occur in stochastic simulations, even when the underlying deterministic model converges to an equilibrium (Fig. 1). Such oscillations still retain many features of the deterministic model, both in their average value and in the approximate length of the cycles (Fig. 3d); the dependence of cycle length on parameters has been investigated in Rosà and Pugliese (2002).

Our study then confirms the well-known effect (Bartlett, 1960; Nisbet and Gurney, 1982; Kaitala *et al.*, 1996) that adding noise (either as demographic or environmental stochasticity) to deterministic models may yield apparently sustained oscillations, even when only damped oscillations exist in the deterministic model (see Aparicio and Solari, 2001, for some analysis of this effect in epidemic models).

The best established examples of population cycles induced by macroparasites is the *T. tenuis*-red grouse system (Hudson *et al.*, 1998). Our simulations, for the parameter values relative to the red grouse system, show cycles with length ranging (Fig. 3 with h=11) between 5.5 and 9 years. This difference in estimated cycle length among the simulations gives the range of uncertainties in model predictions: even if all important factors were known and modelled, and all parameters were exactly estimated, demographic stochasticity will cause such uncertainties; remember that in our simulations the population carrying capacity was just little more than 100 individuals (Tab. 2), and that in a larger population demographic stochasticity would be less important. The cycle lengths from simulations are somewhat higher than the cycle length estimated from actual data (Potts *et al.*, 1984); reasons for this discrepancy may come from the different technique used for estimating cycle length, or from the errors in parameter estimates (the approximation of cycle length shown in Rosà and Pugliese, 2002, gives evidence of which parameters affect most cycle length), or from the lack of relevant factors in the models considered here.

Another important aspect of stochastic simulations is the persistence of the host-parasite system. As shown in Section 3, all simulations of the basic model for the chamois parameter set persisted over a 100 year period, while only about 1% of those for the red grouse parameter set persisted, and none at all for the rock partridge parameter set. We chose 100 years as the reference time interval, but we believe that qualitative results would not change using a different reference interval.

Note that, for the parameter values of Table 2, the values of the basic reproduction ratio R_0 (Rosà and Pugliese, 2002) are around 2 for all the three systems. Hence, while $R_0>1$ is a necessary condition for persistence of a host-parasite system, it appears that the host carrying capacity has a very strong influence on the extinction probability (see, for instance, Hakoyama and Iwasa, 2000): the extinctions found in the simulations for the red grouse and rock partridge systems are certainly favoured by the low values of the carrying capacity of these populations. In fact, since in the low part of host-parasite cycles a very low level of parasite burden is often predicted by the model, one expects that at that moment very few adult parasites are present in the populations, and thus demographic stochasticity easily yields parasite extinction in a short period. Furthermore, the difference in the extinction probability between the red grouse and the rock partridge set is perhaps due to the higher mortality rates both of hosts and of parasites in the rock partridge set.

As already discussed, no simulations persisted over 100 years for the parameter values of the rock partridge system; always, the whole parasite population went extinct in the lower part of some cycle. It is clear from the discussion above that this problem could be solved by increasing the carrying capacity of the host population but, as already explained, our choice was based on the densities reported from field observation.

We prefer to think of other explanations for the persistence of rock-partridge-*A. compar* system, already examined in the previous Sections.

As shown in Section 4, density-dependence in parasite fertility and/or mortality helps population persistence: even a weak dependence could prevent very large increases in the parasite populations and the consequent big crashes of the host population. We have however seen that, even setting the parameters that regulate density-dependence at the values most favourable to persistence, no simulations (out of 1000) persisted longer than 110 years. It seems unlikely that density-dependence by itself makes such a system persist.

Otherwise, persistence could occur at the metapopulation level with several small host populations connected through migration. Persistence in such a system is much easier, since cycle synchronization would decrease with distance (Ranta *et al.*, 1995; Ranta *et al.*, 1997) and then recolonization could occur. But this does not seem to be a significant factor for rock partridge in Trentino (Northern Italy). In fact, Cattadori *et al.* (2000) showed that the rock partridge populations exhibit a sedentary pattern, particularly in comparison with the other galliform species present in the area.

A third reason for host-parasite persistence could be the presence of another host species that acts as a reservoir for the parasites.

Some field observations seem to support this hypothesis for the rock-partridge – *A. compar* in Trentino region. In fact, *A. compar* was also found abundant in black grouses (*Tetrao tetrix*) in Trentino region where black grouse share the same habitat of rock partridge. A first analysis of the data shows that a higher *A. compar* burden is observed in rock partridge population when the black grouse is recorded within the same habitat unit. Moreover, rock partridge populations are more likely to cycle when they share the habitat with black grouse (*Tetrao tetrix*). (Rizzoli *et al*., unpublished data).

We have then explored, through simulations, the hypothesis that *A. compar* persists in Trentino as a parasite of black grouse, while rock partridge is only an additional host. For the sake of simplicity, we took the black grouse population (which is much larger than

that of rock partridges) as constant, as well as its parasite burden; then, we studied the rock partridge population assuming that there is a constant influx of infecting stages coming from the black grouse population into the pool of infecting stages that can be picked up by rock partridges. Our simulations yield the probability of host extinction under different levels of external infection (Fig. 6); for instance, if the carrying capacity is equal to 75 and on average every year 10 infecting free-living stages generated by adult parasites in black grouse interact with the rock partridge population, there is already a 40% probability that the rock partridge becomes extinct over a 100 year interval.

As can be seen from this number (that serves merely as an illustration of the phenomenon), the presence of an external reservoir would make the impact of *A. compar* very dangerous for the long-time survival of rock partridge population; in fact, while a specialised parasite is unlikely to cause host extinction, because its population would drop down when the host population is at low levels, a generalist parasite does not suffer from this problem and may easily have the potential for causing the extinction of a host species (McCallum and Dobson, 1995).

Further investigation and more detailed and specific models will be necessary in order to verify the occurrence of an 'apparent' competition between black grouse and rock partridge mediated by *A.compar* in Trentino region.

It has to be remarked that our simulations neglect the presence of free-living larvae: infections are modelled as if eggs from an adult parasite were directly transmitted into another host. Free-living stages capable of persisting for a long period before infecting a host would certainly help parasite persistence. Free-living stages for Ascaridiidae may survive for several months in suitable moist condition (Anderson, 2000), while very little is known about their persistence in the environment. We are not able, at the moment, to quantify the impact of this factor on the extinction probability of parasites and hosts.

Finally, an intriguing result that may be of general interest comes from the simulations with external infections: over an intermediate region of the level of external infection f, the extinction probability is more or less constant or even decreases with increasing f, as shown in Figs. 6 and 8.

Two facts may help us understand this peculiar pattern. First of all, for f large enough one has deterministic extinction (in the case of the parameter values of Tab. 2 regarding the rock partridge-*A.compar* we get deterministic extinction for $f \approx 4.85 \cdot 10^6$; note however that this values increases with the carrying capacity of host, for instance when the carrying capacity is doubled, $N_K = 150$, we obtain deterministic extinction when $f \approx 9.7 \cdot 10^6$).

The second fact is that the probability of host extinction in the lower part of a host-parasite cycle depends on the level of the host population at the start of cycle (Fig. 7). In other words, if one introduces few parasites in a given host population, the extinction risk is negligible if that population is at around half its carrying capacity, but becomes significant when it is close to the carrying capacity. In fact, when the initial host population is larger, parasite burden may reach a higher value after parasite introduction in the host population, and then more violent population crashes are possible.

We can then understand the qualitative pattern of the probability of extinction curve from the existence of different dynamical patterns in the simulations at different values of f (Fig. 9). When, for low values of f, the host population is almost always parasite-free, increasing f increases the frequency of infections, and hence the overall extinction probability. When f is in the region where parasite-free periods are so short that the host population does not have time to reach the carrying capacity (Fig. 9a), increasing f increases the frequency of infection events, but decreases the risk of extinction in each of these, so that overall extinction probability may not change consistently. When f moves to

the region where parasites are almost always present at low levels (Fig. 9b), extinctions become infrequent. Finally, increasing f even further, we approach the region of deterministic decline of the host population, where the probability of infection is 1.

Summarizing, we have seen that the impact of increasing parasite transmission among different host species may strongly depend on the level of connectivity already existing among these species. We plan to explore further this effect in other host-parasite models. We believe that, when f is in the region below deterministic extinction, this pattern is completely due to stochastic reasons, related to the finite number of hosts and parasites: in fact, the deterministic model (VarAExtInf) does not exhibit any such behaviour, either at equilibrium, or in the transient phase.

It has to be remarked that the peculiar pattern of the curve relating level of external infection to probability of extinction may be less evident if there is density-dependence in the demographic parameters of parasites. In fact, as observed in Section 4, parasites' density-dependence is a strongly stabilizing process for the system; hence, parasites cannot reach very high peaks in abundance and consequently the drastic crashes, that occur at low values of f, of the host population are avoided.

The simulations we considered are very simple, since we assumed homogeneous mixing of host and parasite, neglecting spatial and social structure of hosts, changes with time in environmental factors, as well as acquired immunity to parasitisms. These simulations can however be the basis on which more complex simulations can be built, as well as the reference against which their results may be assessed.

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Thresholds for Disease Persistence in Models for Tick-Borne Infections Including Non-Viraemic Transmission, Extended Feeding and Tick Aggregation

by

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4.0 Abstract

Lyme disease and Tick Borne Encephalitis (TBE) are two emergent tick borne diseases transmitted by the widely distributed European tick *Ixodes ricinus*. The life cycle of the vector and the number of hosts involved requires the development of complex models which consider different routes of pathogen transmission including those occurring between ticks that co-feed on the same host. Hence, we consider here a general model for tick-borne infections. We assumed ticks feed on two types of host species, one competent for viraemic transmission of infection, the second incompetent but included a third transmission route through non-viraemic transmission between ticks co-feeding on the same host. Since a blood-meal lasts for several days these routes could lead to interesting nonlinearities in transmission rates, which may have important effects.

We derive an explicit formula for the threshold for disease persistence in the case of viraemic transmission, also for the case of viraemic and non-viraemic transmission. From this formula, the effect of parameters on the persistence of infection can be determined. When only viraemic transmission occurs, we confirm that, while the density of the competent host has always a positive effect on infection persistence, the density of the incompetent host may have either a positive effect, by amplifying tick population, or a negative ("dilution") effect, by wasting tick bites on an incompetent host. With non-viraemic transmission, the "dilution" effect becomes less relevant. On the other hand, if the nonlinearity due to extended feeding is included, the dilution effect always occurs, but often at unrealistically high host densities.

Finally, we incorporated the effects of tick aggregation on the hosts and correlation of tick stages and found that both had an important effect on infection persistence, if non-viraemic transmission occurred.

4.1 Introduction

Tick borne diseases, such as Lyme disease and Tick-Borne Encephalitis (TBE), have become a significant problem to human populations inhabiting woodland areas in many parts of Europe, the former USSR and North America.

The increase in prevalence of these diseases, not recorded more than 30 years ago, is probably associated with the abandonment of fields and pastures coupled with the expansion of woodland which have favoured the spread and the increase in the densities of both deer and rodents. Hence, tick populations have increased and with them their potential for disease transmission. This increased tick population coupled with people having more leisure time has lead to an increase in the exposure of people to infection.

Concern over tick-borne diseases has stimulated the development of several mathematical models for either tick-borne infections, or tick population dynamics. The important first step was to develop mathematical models for tick population dynamics (e.g. Sandberg *et al.*, 1992; Kitron and Mannelli, 1994; Randolph and Rogers, 1997).

The second to develop models for tick-borne infections and these have often been set, for ease of analysis, in continuous time: see, for instance, Hudson *et al.* (1995) and O'Callaghan *et al.* (1998). Norman *et al.* (1999) and more recently Gilbert *et al.* (2001) proposed a model where ticks are subdivided in the three stages (larvae, nymphs and adults) with stage progression only through a blood meal on a vertebrate host and transmission is only viraemic (i.e., from infected tick to susceptible host, and vice versa). They computed the value of the basic reproduction number, R_0, and showed the so-called dilution effect: when two alternative hosts exist for ticks, only one of which is competent for transmission (e.g. mice and deer for Lyme diseases) an increase in the density of the incompetent host (deer in this example) may shift R_0 from above to below 1, and thus cause pathogen extinction. A similar model has been applied by Caraco *et al.* (1998) to the

deer, tick Borrellia system in the USA, while qualitatively similar results have been obtained by Van Buskirk and Ostfeld (1995) and Mannelli (in press) in computer-based models.

It has been demonstrated in a number of tick borne systems that certain tick hosts, which do not produce a viraemic response, will permit non-viraemic transmission between co-feeding ticks (Jones *et al.*, 1987; Labuda *et al.*, 1993; Odgen *et al.*, 1997). Moreover, Randolph *et al.* (1996, 1999, 2002) have shown the importance of co-feeding (transmission between ticks feeding together on an incompetent host) and temporal coincidence of different tick stages in the maintenance of Tick Borne Encephalitis.

In this paper we build on the model by Norman *et al.* (1999). We introduce general rules for the encounter rates between hosts and ticks, that take into account the duration of feeding. More importantly, we consider specifically the possibility of non-viraemic transmission which is thought to be crucial in the maintenance of several infections such as TBE. We also consider the distribution of tick stages among hosts, which will have extremely important effects on transmission via co-feeding. In fact, in certain parts of the vector's range, patterns of tick infestation on hosts (e.g. rodents) are such that they facilitate co-feeding transmission. Specifically, both immature tick stages show highly aggregated distribution on their host and these aggregated distributions are coincident rather than independent (Perkins *et al.*, in press); those hosts which were feeding larvae were simultaneously feeding the greatest number of nymphs. As a result, about 20% of hosts feed about three-quarters of both larvae and nymphs and the number of susceptible larvae feeding alongside potentially infected nymphs is twice as many as it would be if the distribution were independent (Randolph *et al.*, 2002; Perkins *et al.*, in press).

For these different models we compute, using matrix theory, the threshold quantity for infection persistence. Thus, we may understand the effect of different parameters on disease persistence.

4.2 The model

Following Norman *et al.* (1999), ticks were classified according to their stage as larvae (L), nymphs (N), and adults (A). Each immature stage (larvae and nymphs) requires a blood meal from a suitable vertebrate host. The adult female requires a meal before producing eggs. The model considers two type of hosts: viraemic hosts (H_1) that acquire and transmit the disease, and non-viraemic hosts (H_2) that simply sustain the tick population without amplifying the pathogen. Here, H_2 is assumed to be at constant density while H_1 hosts are classified as being either susceptible (H_{1s}), infected (H_{1i}) or immune (H_{1r}), and their density may vary as a consequence of infection. We assume no trans-ovarial transmission of infection in ticks (reported as negligible in TBE but can not recall reference), while the pathogen is transmitted inter-stadially, so once an immature stage is infected the subsequent stages can transmit the pathogen to a susceptible host. Then, nymphs and adults are classified as either susceptible (N_s and A_s) or infected (N_i and A_i). In the model, the principal route of infection is viraemic transmission, we also consider non-viraemic transmission since there is growing evidence that this is crucial in several tick borne diseases (Randolph *et al.*, 2002).

4.2.1 Tick-hosts interactions

Ticks change stage by feeding on a host, hence, a key factor in the dynamics is the encounter rate between hosts and ticks (in the different stages). We assume throughout a mass-action law, that is, the encounter rate between hosts (whose density will be denoted by H) and, for instance, nymphs will be proportional to the product HN_Q, where N_Q, denotes the density of questing nymphs. In a complete model, we may include N_F (the

density of feeding nymphs) and N_Q as variables, as done by Mwambi et al. (2000) which consider only tick population dynamics. In the simplest approximation, it has instead often been assumed (Caraco et al., 1998; Norman et al., 1999) that both are proportional to the density N of ticks. As an intermediate step, we use here a quasi-steady-state assumption (see Segel and Slemrod, 1989). Assuming that questing nymphs become feeding nymphs by encountering hosts (at rate β^N), and that feeding nymphs drop off hosts at rate σ^N (so the average duration of a blood meal is $1/\sigma^N$). Then we have the equations:

$$\dot{N}_{F_j} = \beta_j^N H_j N_Q - \sigma_j^N N_{F_j} = \beta_j^N H_j (N - N_{F_1} - N_{F_2}) - \sigma_j^N N_{F_j} \tag{1}$$

where N_{F_j} represents the density of nymphs which are feeding on host H_j with $j=1,2$ (definition of all the parameters are shown in Table 1). We assume now that the feeding process is faster than all other processes (deaths, births, stage progression), so that we set $\dot{N}_{F_j} = 0$ and from (1) we obtain

$$N_{F_j} = \frac{c_j^N H_j N}{1 + c_1^N H_1 + c_2^N H_2} \quad \text{and} \quad N_Q = \frac{N}{1 + c_1^N H_1 + c_2^N H_2} \tag{2}$$

where $c_j^N = \beta_j^N / \sigma_j^N$.

From these assumptions, we can write equations for the densities of each stage. For instance, we obtain

$$\frac{dA}{dt} = m^N (\beta_1^N H_1 + \beta_2^N H_2) \frac{N}{1 + c_1^N H_1 + c_2^N H_2} - (\beta_1^A H_1 + \beta_2^A H_2) \frac{A}{1 + c_1^A H_1 + c_2^A H_2} - b_T A,$$

where the first term represents the nymphs becoming adults, the second term the adults that start a blood meal and therefore exit the compartment (it is assumed here that adults reproduce only once in their life, as is usual in the *Ixodidae* ticks) and the third the deaths of questing adults (b_T is ticks' death rate, assumed to be the same in all stages).

TABLE 1. Notation used to denote the various variable and parameters included in the model

Variable or rate	Description
L	Larval density
N	Nymph density
A	Adult density
$T=(L+N+A)$	Total tick density
H_1	Total viraemic host density
H_{1s}	Susceptible viraemic host density
H_{1i}	Infected viraemic host density
H_{1r}	Immune viraemic host density
H_2	Non-viraemic host density
a_T	Birth rate of larvae per adult tick
b_T	Natural death rate of ticks (the same for all stages)
a_1	Birth rate for viraemic host
b_1	Natural rate for viraemic host
α	Rate at which viraemic hosts die from the disease
γ	Rate at which viraemic hosts recover to immunity
β_j^z	Encounter rate between questing ticks in stage z ($z=L,N,A$) and hosts H_j ($j=1,2$)
σ_j^z	Dropping rate of ticks in the stage z ($z=L,N,A$) feeding on host H_j ($j=1,2$)
c_j^z	$=\beta_j^z/\sigma_j^z$ for $z=L,N,A$ and $j=1,2$
ψ^z	$=1/(1+c_1^z H_1 + c_2^z H_2)$ for $z=L,N,A$
g^z	$=\psi^z(\beta_1^z H_1 + \beta_2^z H_2)$ for $z=L,N,A$
m^z	Moulting success probability for ticks in stage z ($z=L,N$)
p^N	Probability of becoming infected for a nymph feeding on an infectious host
p^A	Probability of becoming infected for an adult feeding on an infectious host
q^N	Probability of becoming infected for a viraemic host bitten by an infectious nymph
q^A	Probability of becoming infected for a viraemic host bitten by an infectious adult
λ_{NL}	Non-viraemic transmission coefficient for infected nymphs and larvae
λ_{AL}	Non-viraemic transmission coefficient for infected adults and larvae
λ_{NN}	Non-viraemic transmission coefficient for infected nymphs and susceptible nymphs
λ_{AN}	Non-viraemic transmission coefficient for infected adults and susceptible nymphs
k^L	Aggregation parameter of the Negative Binomial distribution for larvae
k^N	Aggregation parameter of the Negative Binomial distribution for nymphs
k^A	Aggregation parameter of the Negative Binomial distribution for adults
ρ_{NL}	Correlation coefficient for nymphs and larvae
ρ_{AL}	Correlation coefficient for adults and larvae
ρ_{AN}	Correlation coefficient for adults and nymphs

The parameters m^N represent the probability of moulting success for nymphs after feeding. In practise, m^N may depend on the host species (Humair *et al.*, 1999) so to be accurate we should use m_1^N and m_2^N. However, when we do, the formulae become awkward, and so in this presentation we stick to the case of a single m^N. For ease of notation, it will be convenient to introduce the following functions:

$$\psi^z(H_1, H_2) = \frac{1}{1 + c_1^z H_1 + c_2^z H_2} \text{ and } g^z(H_1, H_2) = \frac{\beta_1^z H_1 + \beta_2^z H_2}{1 + c_1^z H_1 + c_2^z H_2},$$

where $z = L$, N or A. Note that if $\beta_j^z H_j << \sigma_j^z$ (as it appears likely) the functions ψ^z are very close to 1, so that g^z are practically linear over most of the reasonable range of H_1 and H_2.

4.2.1.1 Density-dependence in ticks and hosts

Detecting density-dependence in the demographic parameters of ticks is rather complex because of the complexity of their life cycle (Hudson *et al.*, 2002). However, without introducing any density-dependent factor, the tick population would grow (or decrease) exponentially unrealistically making it difficult to identify any meaningful persistence threshold.

Randolph and Rogers (1997) present a model where the mortalities of the larval-to-nymph and nymphal-to-adult stages are a function of the initial densities of larvae and nymphs respectively.

Here, for the sake of simplicity, we assume, like Norman *et al.* (1999), that only the production of larvae per feeding adult tick $a_T(T)$ is density-dependent, where $a_T(T)$ is a decreasing function of the total number of ticks present in the system. Furthermore, to simulate logistic growth of the viraemic host H_1 (the non- viraemic host is assumed to be at a constant size H_2) we assumed that the birth rate $a_1(H_1)$ is a decreasing function of the

total density, while the death rate b_1 is assumed to be constant. The effect of these assumptions is examined in the Discussion.

4.2.2 Infection

4.2.2.1 Viraemic transmission

Initially, we model viraemic transmission as in Norman *et al.* (1999). In particular, we assume that viraemic transmission can occur only on one species of host, usually H_1. We assume that a proportion q^z of the hosts being bitten by infected ticks become infected; here z may be equal to N or A, since questing larvae cannot pass on virus until they become nymphs.

Hence, the rate at which susceptible hosts become infected will be equal to:

$$q^N \beta_1^N H_{1s} N_i \psi^N (H_1, H_2) + q^A \beta_1^A H_{1s} A_i \psi^A (H_1, H_2),$$

where H_{1s} is the density of susceptible hosts, N_i and A_i those of infected nymphs and adults.

Analogously, we assume that a proportion p^z of ticks (here z may be equal to L or N) become infected while feeding on hosts and then switching from larvae to infected nymphs or from susceptible nymphs to infected adults. Hence, the rate at which larvae become infected will be equal to

$$m^L p^L \beta_1^L H_{1i} L \psi^L (H_1, H_2),$$

and the rate at which susceptible nymphs become infected will be equal to

$$m^N p^N \beta_1^N H_{1i} N_s \psi^N (H_1, H_2),$$

where H_{1i} is the density of infected hosts, L and N_s those of larvae and susceptible nymphs respectively, while m^z is the probability of moulting success for ticks in stage z (z=L,N).

4.2.2.2 Non-viraemic transmission

Modelling the rate of non-viraemic transmission adds another level of complexity, but a level we suspect is important. It is reasonable to assume that, once a susceptible nymph (for instance) arrives on a host it may be infected, with a certain probability, by a feeding infected tick presents on the same host over the whole duration of the blood-meal. Hence, the rate at which nymphs (for instance) get infected through the co-feeding route will be the product of the encounter rate of susceptible nymphs and this probability. We have already considered the first term. To compute the second we assume that the probability of getting infected will depend on the mean number of infected ticks present on the same host of a given feeding nymph.

Now, it is easy to see that the mean number of nymphs present on a random host will be equal to the number of feeding nymphs, given by expression (2), over the number of hosts. However, the mean number of other nymphs present on the same host of a given feeding tick may be different from the mean number of nymphs present on a given host. To understand that from a statistical point of view, let p_i be the proportion of hosts carrying i nymphs; then, the probability that, on the same host of a randomly selected feeding nymph, there are i nymphs (including the one from which we started) is $q_i = \dfrac{ip_i}{\sum_l lp_l}$; in fact, we select a nymph at random and so it will be more likely to find a host that carries many nymphs. The average number of nymphs on that host is therefore

$$\sum_i iq_i = \frac{\sum_i i^2 p_i}{\sum_l lp_l} = \frac{E(N^2)}{E(N)} = E(N) + \frac{V(N)}{E(N)},$$

where $E(N) = \sum_i ip_i$ represents the mean number of nymphs on a randomly selected host, $V(N)$ is the variance of that number. In order to get the mean number of *other* nymphs

present on the same host of a given feeding nymph, we must subtract 1 (the nymph we started with) obtaining

$$E(N) + \frac{V(N)}{E(N)} - 1 . \tag{3}$$

Note that, if the distribution of the nymphs is Poisson, the variance is equal to the mean, and the mean number of other ticks present on the same host of a random feeding nymph is equal to the mean number of nymphs present on a random host. On the other hand, if the distribution were aggregated (for instance, a negative binomial distribution that is described by the mean and the parameter k), then the variance is equal to $V(N)=E(N)(1+E(N)/k)$, so that the mean number of other ticks present on the same host of a given feeding nymph is equal to $E(N)(1+1/k)$. We will follow this latter assumption, which is used in models for macroparasites (Anderson and May, 1978), then the distribution of each stage will be assumed to be a negative binomial with a given k.

Hence, the mean number of infected nymphs on a host 2 on which a nymph arrives is:

$$w = c_2^N N_i \psi^N (H_1, H_2)(1 + 1/k^N) .$$

The probability that this susceptible nymph does not get infected by co-feeding infected nymphs can be approximated as $exp(-\lambda_{NN} w)$, where λ_{NN} is a proportionality constant that includes the probability for a nymph of being in a co-feeding group, the probability of being infected in that case and the probability of the infection being maintained trans-stadially. Clearly, one could also include the last factor of w in λ_{NN} but we preferred to keep it apart , to explore the role of aggregation.

Putting all the ingredients together, the encounter rate of susceptible nymphs with hosts of species 2 is $\beta_2^N H_2 N_s \ \psi^N (H_1, H_2)$, the probability of getting infected is $1 - exp(-\lambda_{NN} w)$, so that the rate at which nymphs get infected by other nymphs through co-feeding is:

$$m^N \beta_2^N N_s H_2 \, \psi^N (H_1, H_2)[1 - exp\{-\lambda_{NN} c_2^N N_i \psi^N (H_1, H_2)(1 + 1/k^N)\}]. \tag{4}$$

When we consider inter-stadial (for instance, nymphs to larvae) transmission by co-feeding, we need to know the mean number of infected nymphs on the same host of a given feeding larva. Let p_{ij} be the proportion of hosts carrying i larvae and j nymphs; then the probability that the host on which a given larva is feeding will carry i larvae and j nymphs is equal to $\dfrac{i p_{ij}}{\sum_{k,l} k p_{kl}}$. Hence, the average number of nymphs on that host is equal to

$$\frac{\sum_{i,j} i j p_{ij}}{\sum_{k,l} k p_{kl}} = \frac{E(LN)}{E(L)} = E(N) + \frac{Cov(L,N)}{E(L)}. \tag{5}$$

As expected, the mean number of nymphs on the same host of a given feeding larva is influenced by the covariance between larvae and nymphs. To proceed, we assume that the association between stages are fixed constants; moreover the assumption that each stage is distributed in a negative binomial with fixed parameter means

$$V(t) = E(t) + \frac{(E(t))^2}{k} \cong \frac{(E(t))^2}{k};$$

so, from (5) we obtain

$$E(N) + \frac{Cov(L,N)}{E(L)} = E(N) + \frac{\rho_{LN}\sqrt{V(N)V(L)}}{E(L)} \cong E(N) + \frac{\rho_{LN}E(N)}{\sqrt{k^L k^N}} = E(N)(1 + \rho_{LN}/\sqrt{k^L k^N}).$$

We can then say that the rate at which larvae get infected by nymphs through co-feeding is

$$m^L \beta_2^L L H_2 \, \psi^L (H_1, H_2)[1 - \exp\{-\lambda_{NL} c_2^N N_i \psi^N (H_1, H_2)(1 + \rho_{LN}/\sqrt{k^L k^N})\}] \tag{6}$$

where λ_{NL} has the same interpretation as λ_{NN}. Note that, formally, (4) is a special case of (6) with $\rho_{NN} = 1$.

4.2.3 The equations

From the previous assumptions, we obtain the following equations:

$$
\begin{cases}
\dfrac{dL}{dt} = g^A(H_1,H_2)a_T(T)(A_i+A_s) - b_T L - g^L(H_1,H_2)L \\[2mm]
\dfrac{dN_s}{dt} = m^L g^L(H_1,H_2)L - m^L \beta_1^L p^L H_{1i}\psi^L(H_1,H_2)L - b_T N_s - g^N(H_1,H_2)N_s + \\[2mm]
\qquad - m^L \beta_2^L LH_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{NL}c_2^N N_i \psi^N(H_1,H_2)(1+\rho_{LN}/\sqrt{k^L k^N})\}] + \\[2mm]
\qquad - m^L \beta_2^L LH_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{AL}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AL}/\sqrt{k^L k^A})\}] \\[2mm]
\dfrac{dA_s}{dt} = m^N g^N(H_1,H_2)N_s - m^N \beta_1^N p^N H_{1i}\psi^N(H_1,H_2)N_s - b_T A_s - g^A(H_1,H_2)A_s + \\[2mm]
\qquad - m^N \beta_2^N N_s H_2\,\psi^N(H_1,H_2)[1-\exp\{-\lambda_{NN}c_2^N N_i \psi^N(H_1,H_2)(1+1/k^N)\}] + \\[2mm]
\qquad - m^N \beta_2^N N_s H_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{AN}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AL}/\sqrt{k^N k^A})\}] \\[2mm]
\dfrac{dN_i}{dt} = m^L p^L \beta_1^L H_{1i}\psi^L(H_1,H_2)L - b_T N_i - g^N(H_1,H_2)N_i + \\[2mm]
\qquad + m^L \beta_2^L LH_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{NL}c_2^N N_i \psi^N(H_1,H_2)(1+\rho_{LN}/\sqrt{k^L k^N})\}] + \\[2mm]
\qquad + m^L \beta_2^L LH_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{AL}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AL}/\sqrt{k^L k^A})\}] \\[2mm]
\dfrac{dA_i}{dt} = m^N p^N \beta_1^N H_{1i}\psi^N(H_1,H_2)N_s + m^N g^N(H_1,H_2)N_i - b_T A_i - g^A(H_1,H_2)A_i + \\[2mm]
\qquad + m^N \beta_2^N N_s H_2\,\psi^N(H_1,H_2)[1-\exp\{-\lambda_{NN}c_2^N N_i \psi^N(H_1,H_2)(1+1/k^N)\}] + \\[2mm]
\qquad + m^N \beta_2^N N_s H_2\,\psi^L(H_1,H_2)[1-\exp\{-\lambda_{AN}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AL}/\sqrt{k^N k^A})\}] \\[2mm]
\dfrac{dH_{1i}}{dt} = q^N \beta_1^N H_{1s}\psi^N(H_1,H_2)N_i + q^A \beta_1^A H_{1s}\psi^A(H_1,H_2)A_i - (b_1+\gamma+\alpha)H_{1i} \\[2mm]
\dfrac{dH_{1r}}{dt} = \gamma H_{1i} - b_1 H_{1r} \\[2mm]
\dfrac{dH_{1s}}{dt} = a_1(H_1)H_1 - b_1 H_{1s} - q^N \beta_1^N H_{1s}\psi^N(H_1,H_2)N_i - q^A \beta_1^A H_{1s}\psi^A(H_1,H_2)A_i
\end{cases}
\tag{7}
$$

Most of the assumptions that lead to these equations have already been discussed. In addition, it has been assumed that ticks have no impact on the demography of either H_1 or H_2 (whose density is assumed to be constant), while infected hosts have an additional death rate α. It should also be noted that infected nymphs (and adults) that become infected through co-feeding must be subtracted from susceptible nymphs (or adults) since they

correspond to feeding susceptible larvae (nymphs) that do not develop into susceptible nymphs (adults). The model without non-viraemic transmission analysed by Norman *et al.* (1999) is a special case of the model presented here: one needs only set all parameters λ equal to 0 and $\psi(H_1,H_2)$ equal to 1.

4.3 Basic reproduction numbers (R_0)

R_0 is a measure of the maximum reproductive potential of a parasite between one generation and the next for a susceptible host population in a given environment. R_0 is one of the most important and useful concepts in epidemiology since it determines whether or not a parasite has the potential to spread in a host population, the difficulty of eradication and also produces an estimate of parasite fitness. For microparasites (virus and bacteria), R_0 is defined as the average number of secondary cases which one case can produce in a population consisting only of susceptible individuals. If $R_0 > 1$ a chain reaction of new cases will result leading to an epidemic outbreak, but if $R_0 < 1$ the number of infected hosts will fall and eventually be lost from population.

For macroparasites, and in particular for ticks, the idea of R_0 is the same, but the definition is subtly different. In this instance, R_0 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 (Hudson *et al.*, 2002).

Mathematically, R_0 works as a threshold quantity for the stability of the disease-free equilibrium. In fact, it makes the disease free-equilibrium (for microparasites) or the parasite free-equilibrium (for macroparasites) stable when $R_0 < 1$ or unstable when $R_0 > 1$.

A very useful tool in the computation of the thresholds for disease persistence in epidemic models is the Perron-Frobenius theory (see the application to epidemic models in Diekmann and Heesterbeek, 2000). Using this theory, we derive, in the following sections,

the thresholds for the persistence of both ticks and the disease distinguishing the cases with and without non-viraemic transmission. We will write these in the form $R_0 > 1$ where the R_0 are explicit quantities related to the transmission of the infection. We remark that, although we used the symbol R_0 for these threshold quantities, they are not always exactly equal to the basic reproduction number defined in Diekmann and Heesterbeek (2000) as the spectral radius of the "next-generation matrix". The spectral radius cannot be computed explicitly, and we believe that our quantity has a useful interpretation. In either case, the conditions for persistence are the same with both methods.

4.3.1 The case with only viraemic transmission

Here we consider only the viraemic route of the infection. This means that a susceptible tick can only become infected when feeding on an infected viraemic hosts (H_{1i}). At the same time the transmission could pass from infected ticks to susceptible hosts (H_{1s}) while non-viraemic hosts (H_2) do not take part in the infection process. Thus, in this case we set all of the parameters concerned with non-viraemic transmission to zero ($\lambda_{NL}=\lambda_{AL}=\lambda_{NN}=\lambda_{AN}=0$). The special case with all the quantities $\psi^z(H_1,H_2)=1$ has been already analysed by Norman *et al.* (1999) and Gilbert *et al.* (2001).

Tick-free equilibrium

Through the study of the local stability of the tick-free equilibrium (see Appendix A) we derived the following basic reproduction number for the tick population:

$$R_0^{ticks} = a_T(0)\frac{m^L g^L(H_1,H_2)}{b_T + g^L(H_1,H_2)}\frac{m^N g^N(H_1,H_2)}{b_T + g^N(H_1,H_2)}\frac{g^A(H_1,H_2)}{b_T + g^A(H_1,H_2)}. \tag{8}$$

This quantity represents the threshold condition for the persistence of ticks in the system. When $R_0^{ticks} > 1$ the ticks will persist and, from numerical simulation, it appears that tick and host populations will settle to a positive coexistence equilibrium. The quantity R_0^{ticks} has a

rather obvious biological interpretation in that: if the product of the losses from each tick stage is greater than the product of the gains to each stage, then the ticks will die out, if not, they will persist. In particular, the expression of R_0^{ticks} in (8) is the result of three multiplicative factors whose biological interpretations are the following:

(i) $\dfrac{m^L g^L(H_1, H_2)}{b_T + g^L(H_1, H_2)}$ is the probability of a larva becoming a nymph,

(ii) $\dfrac{m^N g^N(H_1, H_2)}{b_T + g^N(H_1, H_2)}$ is the probability of a nymph becoming an adult and

(iii) $a_T(0) \cdot \dfrac{g^A(H_1, H_2)}{b_T + g^A(H_1, H_2)}$ is the number of larvae produced per adult.

Disease-free equilibrium

Through the study of the local stability of the disease-free equilibrium in the case with only viraemic transmission (see Appendix B) we found that the disease-free equilibrium is stable if and only if the following condition is satisfied:

$$
\begin{aligned}
R_0^{vir} = & \frac{m^L p^L \beta_1^L \psi^L(H_1, H_2)L}{(b_1 + \gamma + \alpha)} \frac{q^N \beta_1^N H_1 \psi^N(H_1, H_2)}{(b_T + g^N(H_1, H_2))} + \\
& + \frac{m^L p^L \beta_1^L \psi^L(H_1, H_2)L}{(b_1 + \gamma + \alpha)} \frac{m^N g^N(H_1, H_2)}{(b_T + g^N(H_1, H_2))} \frac{q^A \beta_1^A H_1 \psi^A(H_1, H_2)}{(b_T + g^A(H_1, H_2))} + \\
& + \frac{m^N p^N \beta_1^N \psi^N(H_1, H_2)N}{(b_1 + \gamma + \alpha)} \frac{q^A \beta_1^A H_1 \psi^A(H_1, H_2)}{(b_T + g^A(H_1, H_2))} < 1.
\end{aligned}
\tag{9}
$$

If we follow an infected host we see that it produces on average $\dfrac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha}$ infected nymphs. Each nymph will infect a host with probability $\dfrac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N}$, and can also develop to infected adult with probability $\dfrac{m^N g^N}{b_T + g^N}$ and then infect a host as adult with probability

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$\dfrac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A}$. Finally, an infected host produces also $\dfrac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha}$ infected adults that

infect a host with probability $\dfrac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A}$.

4.3.2 The case with non-viraemic transmission

Here, we consider horizontal transmission between ticks. This means that a susceptible tick can become infected not only by feeding on an infected viraemic host but also when co-feeding with other infected ticks present on the same non-viraemic host. In our model the parameters measuring non-viraemic transmission are λ_{NL}, λ_{AL}, λ_{NN} and λ_{AN} depending on the different tick stages that are co-feeding (Tab. 1). Through the study of the local stability of the disease-free equilibrium in the case with non-viraemic transmission (see Appendix C) we obtained a joint condition for the stability of the disease-free equilibrium that means disease extinction. The disease-free equilibrium is stable if the following three condition are satisfied:

$$R_{0,ad}^{non-vir} = \frac{m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N (1 + \rho_{AN}/\sqrt{k^A k^N})}{b_T + g^A} < 1, \tag{10}$$

$$R_{0,nym}^{non-vir} = \frac{m^L \beta_2^L c_2^N \lambda_{LN} LH_2 \psi^N \psi^L (1 + \rho_{NL}/\sqrt{k^N k^L})}{b_T + g^N} < 1, \tag{11}$$

$$
\begin{aligned}
R_0^{all} = {}& \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{1}{1 - R_{0,nym}^{non-vir}} \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N} + \\[2mm]
& + \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2 [\psi^N]^2 \left(1 + \dfrac{1}{k^N}\right)}{(b_T + g^N)(1 - R_{0,nym}^{non-vir})} \frac{q^A \beta_1^A H_1 \psi^A}{(b_T + g^A)(1 - R_{0,nym}^{non-vir})} + \\[2mm]
& + \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \frac{1}{1 - R_{0,ad}^{non-vir}} \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} + \\[2mm]
& + \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \frac{m^L \beta_2^L c_2^A \lambda_{AL} LH_2 \psi^A \psi^L \left(1 + \dfrac{\rho_{AL}}{\sqrt{k^A k^L}}\right)}{(b_T + g^A)(1 - R_{0,ad}^{non-vir})} \frac{q^N \beta_1^N H_1 \psi^N}{(b_T + g^N)(1 - R_{0,nym}^{non-vir})} + R_0^{non-vir} < 1,
\end{aligned}
\tag{12}
$$

where

$$R_0^{non-vir} = \frac{m^L \beta_2^L c_2^A \lambda_{AL} L H_2 \psi^A \psi^L (1+\rho_{AL}/\sqrt{k^A k^L})}{b_T + g^A} \frac{m^N \beta_2^N c_2^N \lambda_{NN} N H_2 [\psi^N]^2 (1+1/k^N)}{b_T + g^N} \frac{1}{1-R_{0,nym}^{non-vir}} \frac{1}{1-R_{0,ad}^{non-vir}} \quad (13)$$

Conditions (10) and (11) are threshold conditions for horizontal transmission between ticks. Equation (10) means that each infected adult tick produces less than 1 infected adult tick, by infecting nymphs through co-feeding. Equation (11) analogously means that each infected nymph produces less than 1 infected nymph, by infecting larvae through co-feeding.

The expression of R_0^{all}, shown in (12), is more complex but the terms all have a biological interpretation. The first three terms correspond to those in the reproduction number with only viraemic transmission (see (9)), but they are changed due to non-viraemic transmission. In fact, we must consider that each nymph infected by a host will on average produce $R_{0,nym}^{non-vir}$ infected nymphs by infecting co-feeding larvae that, after moulting, will become infected nymphs; all of these will produce through co-feeding $(R_{0,nym}^{non-vir})^2$ other infected nymphs; summing over all generations of infections, the "progeny" via co-feeding of an infected nymphs is equal to $1/(1-R_{0,nym}^{non-vir})$ infected nymphs (remember that we are under conditions (10) and (11)). Hence, when we count how many infected hosts an infected host produces through infected nymphs and back, we must multiply the average number of infected nymphs produced by an infected host, that is $\frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha}$, by the "co-feeding nymph progeny" of each infected nymph, that is $1/(1-R_{0,nym}^{non-vir})$, by the average number of hosts infected by each nymph, that is $\frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N}$, obtaining thus the first term in (12). The changes in the second and third terms are analogous, noting that now the number of infected adults produced by an infected nymph is not given simply by its

probability of getting to the adult stage, but we must also add the number of adults produced from nymphs by co-feeding. The fourth term is the reciprocal of the second and describes transmission from a host to an adult, then transmission from adults to nymphs by co-feeding, and finally viraemic transmission from nymphs to hosts. The last term, denoted by $R_0^{non-vir}$, computes the total transmission potential (between and within nymphs and adults) of the non-viraemic route. It should be noted that several terms can disappear in the special cases considered below.

4.3.3 Special cases

An interesting special case, based on the transmission dynamics of *Borrelia* or of louping ill, occurs when adult ticks do not feed on H_1 (e.g. mice for *Borrelia*), and larvae do not feed on H_2 (e.g. deer). In this case we have $\beta_1^A = \beta_2^L = 0$ and, as there are no larvae on the non-viraemic host, non-viraemic transmission cannot occur through larvae and consequently λ_{NL} and λ_{AL} will be 0.

Under this assumption the threshold for disease persistence assumes the following form, which is identical to the case with only viraemic transmission:

$$R_0^{vir} = \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \cdot \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N} \tag{14}$$

However, note that we also have the extra condition for stability (see (10) and (11)). In this case we have two separate epidemic processes. The first is through the viraemic (or spirochaetaemic for *Borrelia*) route: infected nymphs biting susceptible hosts which are then bitten by larvae: the threshold condition for this process is $R_0^{vir} > 1$ with R_0^{vir} given in (14). The second epidemic is purely non-viraemic: infected adults infecting susceptible nymphs via co-feeding; the threshold condition for this process is in (10). The second epidemic has no effect on the first, since infected adults do not participate in viraemic

transmission as they do not feed on H_1 (β_1^A =0). Hence, the two threshold conditions can be considered independently. Note, that if R_0 in (14) is less than 1 but (10) is violated, only adult ticks will be infected, while nymphs and hosts will not be infected.

Another interesting special case occurs with only non-viraemic transmission in the system. This means that there are no competent hosts in the system and the reservoir of the diseases are exclusively the ticks. In this case all the parameters concerning the viraemic transmission have to be set to 0. Now, R_0^{all} of (12) reduces to $R_0^{non-vir}$ shown in (13). In this case the disease-free equilibrium is unstable (the pathogen persists in the system) when at least one among $R_{0,nym}^{non-vir}$, $R_{0,ad}^{non-vir}$ or $R_0^{non-vir}$ shown respectively in (10), (11) and (13) is larger than 1. From these expressions it can be seen that a high value of the correlation coefficients ρ, or a low value of the aggregation parameters k, make pathogen persistence more likely. As a consequence, non-viraemic transmission among highly aggregated ticks could be sufficient to make the pathogen persist in the system even without hosts that sustain the infection.

4.4 Results and discussion

4.4.1 Persistence-extinction boundary with only viraemic transmission

If we set R_0^{vir} to 1 in (9) and plot H_1 against H_2 for a chosen set of parameter values we can determine the densities of viraemic and non-viraemic host that must be present for the pathogen to persist (Figs 1A and 1B). Both figures show that a minimum density of viraemic host (H_1) is needed in order to make the pathogen persist in the system.

The effect of the density of non-viraemic hosts H_2 is more complex; in fact, it has already been observed (Norman *et al*., 1999) that their density may have either a positive effect on

infection transmission, by amplifying tick population, or a negative ("dilution") effect, by

wasting tick bites on incompetent hosts. Indeed, the shape of the persistence-extinction

boundary may differ with only slightly changes in the parameter values (see Figs 1A and

1B, which differ only in the value of the encounter rate between questing nymphs and

viraemic hosts, β_1^N). In the case of Fig 1A, only the dilution effect of H_2 occurs: starting

from a point (H_1,0) where R_0^{vir}>1, an increase of the non viraemic hosts makes the R_0^{vir}

decrease till it becomes lower than 1 and the disease dies out; furthermore, if we start from

a point (H_1,0) with R_0^{vir}<1, R_0^{vir} will remain lower than 1 for any density H_2 of the non
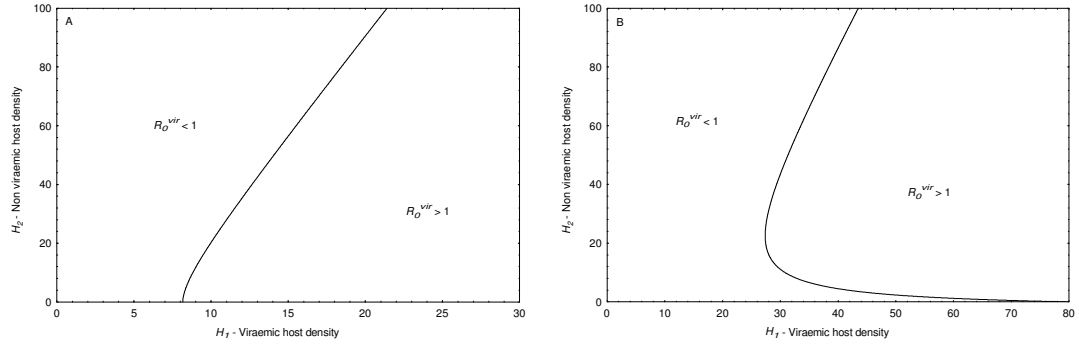
viraemic hosts.

FIG. 1. The effect of hosts densities on R_0^{vir} in the case without non-viraemic transmission. In (A) $\beta_1^N = 10^{-5}$, while in (B) $\beta_1^N = 10^{-6}$. The other parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^L = 10^{-3}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8$, $N = 10^6$, $\gamma = 0.5775$, $\alpha = 2.31$, $b_1 = 0.087$, $b_T = 0.0277$, $q^A = q^N = 1$, $p^L = p^N = 1$, $m^L = m^N = 1$, $\sigma_j^z = 15$, $\lambda_{NL} = \lambda_{AL} = \lambda_{NN} = \lambda_{AN} = 0$. The parameter values are purely illustrative, though elaborated from Hudson *et al.* (1995) and Norman *et al.* (1999), measuring time in months and densities in km^{-2}.

In Fig 1B, if we start from a point (H_1,0) with H_1 in an intermediate region (between 30

and 60), an initial increase of H_2 makes the pathogen persist (R_0^{vir} moves from below 1 to

above 1) but a further increase of H_2 causes a decrease of R_0^{vir} and again the dilution effect

of H_2 is observed.

We then see that the net effect of H_2 on R_0^{vir} depends on the quantitative strength of the two effects, and it is difficult to predict the outcome *a priori*. One may note that the decrease of β_1^N of an order of magnitude from Fig. 1A to 1B makes the ticks more dependent on H_2 for amplification; thus, it is not surprising the positive effect of H_2 on R_0^{vir} is more apparent in Fig. 1B.

4.4.2 Effect of non-viraemic transmission

From the expression of R_0^{all} in (12) with non-viraemic transmission we see that the effect of non-viraemic transmission terms is to increase the basic reproduction number of the disease.

In terms of host densities, the boundary between the persistence and extinction regions in the *(H_1,H_2)*-plane shifts upwards and to the left with increasing non viraemic terms (see Fig. 2, where the effect of λ_{AN}, the parameter of non-viraemic transmission between nymphs and adults, is shown; the other parameters have a similar effect).
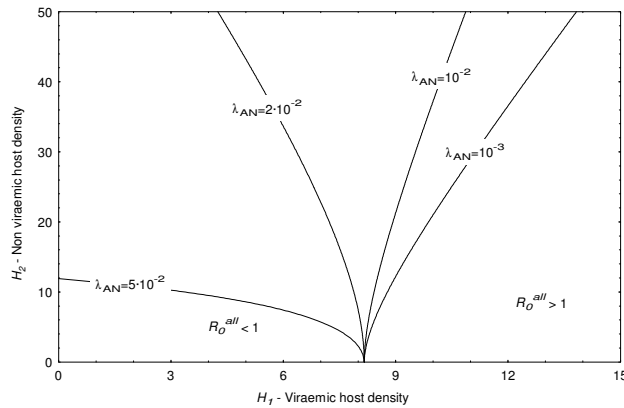

FIG. 2. Effect of non-viraemic terms λ_{AN} on R_0^{all}. The other non-viraemic terms are set to 0 and the rest of parameters are: $\beta_1^L=10^{-5}$, $\beta_1^N=10^{-5}$, $\beta_1^A=10^{-5}$, $\beta_2^L=10^{-3}$, $\beta_2^N=10^{-3}$, $\beta_2^A=10^{-3}$, $L=10^8$, $N=10^6$, $\gamma=0.5775$, $\alpha=2.31$, $b_1=0.087$, $b_T=0.0277$, $q^A=q^N=1$, $p^L=p^N=1$, $m^L=m^N=1$, $\sigma_j^z=15$, $k^N=\infty$, $\rho_{NL}=\rho_{AN}=\rho_{AL}=0$.

For high enough values of the non-viraemic terms, the dilution effect completely disappears and the disease can persist in the absence of the viraemic host. The effect of all the non-viraemic terms on R_0^{all} are explored in Fig. 3. R_0^{all} increases particularly when terms involving the larval stage (λ_{AL} and λ_{NL}) are included in the model. This is quite understandable, since a tick which is infected as a larva will have two opportunities to transmit the infection, while a tick infected as a nymph will have just one opportunity.
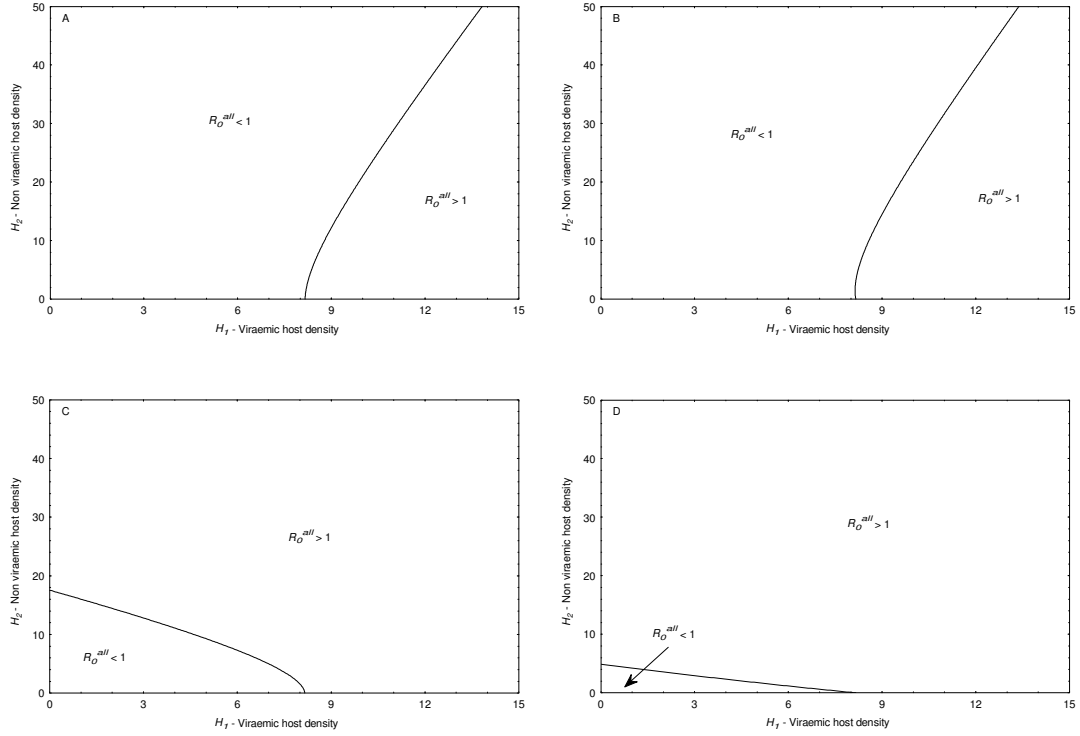

FIG. 3. Effect of different non-viraemic terms on R_0^{all}. The effect of λ_{AN} is shown in figure 3A, λ_{NN} in 3B, λ_{AL} in 3C and λ_{NL} in 3D. In all the figures the non-viraemic term takes the values 10^{-3}, while the others are set to 0. The other parameters are: $\beta_1^L=10^{-5}$, $\beta_1^N=10^{-5}$, $\beta_1^A=10^{-5}$, $\beta_2^L=10^{-3}$, $\beta_2^N=10^{-3}$, $\beta_2^A=10^{-3}$, $L=10^8$, $N=10^6$, $\gamma=0.5775$, $\alpha=2.31$, $b_I=0.087$, $b_T=0.0277$, $q^A=q^N=1$, $p^L=p^N=1$, $m^L=m^N=1$, $\sigma_j^z=15$, $k^N=\infty$, $\rho_{NL}=\rho_{AN}=\rho_{AL}=0$.

Now, if we further increase the density of non-viraemic host H_2 in Fig. 3C (the same happens for Fig. 3D) we obtain the situation shown in Fig. 4, where for very high values of H_2 (note the logarithmic scale of H_2 axis), R_0 always drops below 1. This is because for so high values of H_2 the functions ψ^z become significantly less than 1 and the nonlinearity

due to extended feeding has a strong effect on R_0. Biologically this is because with a very high density of non-viraemic hosts, almost all ticks will feed on H_2 hosts, but each individual host will be carrying very few ticks, so that the probability of finding co-feeding ticks will be relatively low; hence, non-viraemic transmission will become insignificant while viraemic transmission on H_2 hosts is, by assumption, impossible. However, for these parameters the host densities at which this effect occurs are unrealistically high, so that this effect, whilst interesting mathematically, is in this case practically irrelevant.
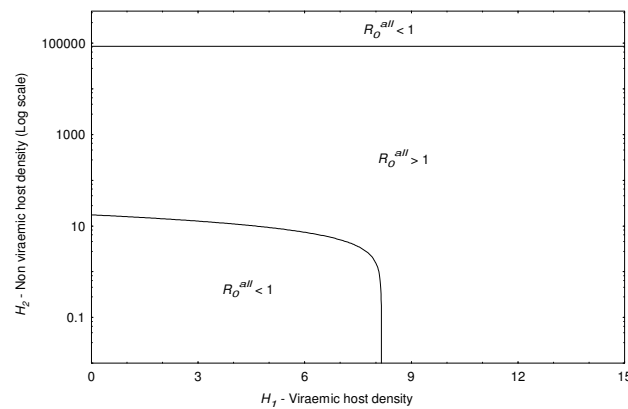

FIG. 4. Effect of extended feeding on R_0^{all} for high values of non-viraemic host, H_2. The parameters values are the same of those in Fig. 3C (λ_{AL}>0).

4.4.3 Effect of aggregation on **R$_0$**

We have not yet considered either the aggregation of the tick distribution among hosts or the correlation between different stages of ticks feeding on the same host in the figures presented in the previous sections. However, it is well known in the literature (see, for instance, Randolph *et al.*, 2002) that each tick stage shows highly aggregated distributions on their host population; moreover, these aggregated distributions are coincident rather than independent: those hosts feeding large number of larvae were simultaneously feeding the greatest number of nymphs. It has been surmised that this pattern of tick infestation facilitates transmission via co-feeding and thus significantly increases the basic

reproductive number R_0 of the pathogen (Randolph *et al.*, 1999). In Figs 5 and 6 we show the quantitative effect of tick distribution on R_0^{all} for the parameter values used in Fig. 3. Fig. 5 corresponds to Fig. 3B with H_1 fixed at 10; hence, we are in the region where the dilution effect holds: increasing the density of H_2 would make R_0^{all} drop below 1; as can be seen in Fig. 5, a strong aggregation in nymph distribution ($k^N<<1$) increases significantly R_0^{all} and may double the density of H_2 at which the dilution effect occurs.
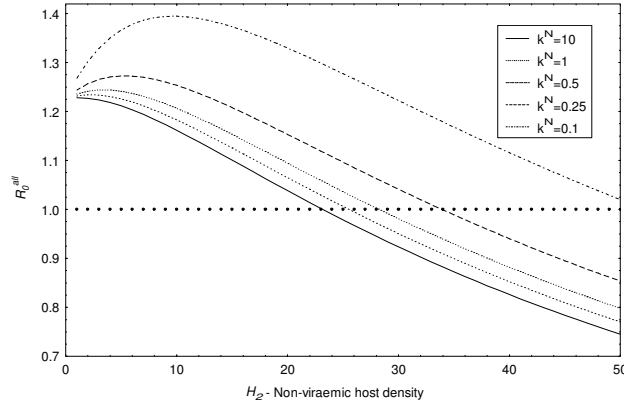

FIG. 5. Graph to show the effect of H_2 on R_0^{all} for different values of k^N, when H_1 is supposed to be constant (in this case H_1=10). λ_{NN}=5·10^{-5}, while the other non-viraemic terms are set to 0. The other parameters are: β_1^L=10^{-5}, β_1^N=10^{-5}, β_1^A=10^{-5}, β_2^L=10^{-3}, β_2^N=10^{-3}, β_2^A=10^{-3}, L=10^8, N=10^6, γ=0.5775, α=2.31, b_1=0.087, b_T=0.0277, q^A=q^N=1, p^L=p^N=1, m^L=m^N=1, σ=0.5.

FIG. 6. Graph to show the effect of H_2 on R_0^{all} for different values of ρ_{AL}, when H_1 is supposed to be constant (in this case H_1=5). λ_{AL}=5·10^{-5}, k^L=1, k^N=0.1 while the other non-viraemic terms are set to 0. The other parameters are: β_1^L=10^{-5}, β_1^N=10^{-5}, β_1^A=10^{-5}, β_2^L=10^{-3}, β_2^N=10^{-3}, β_2^A=10^{-3}, L=10^8, N=10^6, γ=0.5775, α=2.31, b_1=0.087, b_T=0.0277, q^A=q^N=1, p^L=p^N=1, m^L=m^N=1, σ=0.5.
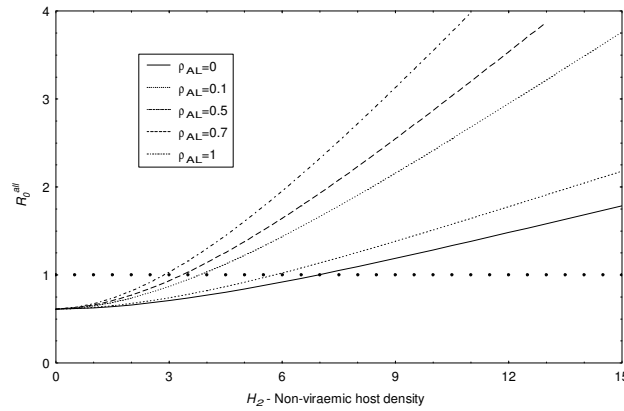
Fig. 6 corresponds to Fig. 3C with H_1=5, where, on the other hand, increasing the density of H_2 makes R_0^{all} grow above 1. In this case, a strong correlation between adults and larvae ($\rho_{AL} \approx 1$) causes a big increase in R_0^{all}.

On the whole, the expressions shown in this paper for the threshold for disease persistence of tick-borne infections clarify the possible role of the different pathways in sustaining the infection, as well as the importance of tick distributions in the case of non-viraemic transmission, and the possible relevance of the encounter rates in the case of multiple hosts. This understanding may help in identifying possible strategies for disease control, and assessing their possible results. Finally, the assumptions made on the density-dependence factors have no real consequence on the threshold quantities computed in the text (although they may affect the overall dynamics of the system). In fact, if a_T were constant, one would only need to substitute this constant for the quantity computed at the relevant equilibrium. Conversely, if some quantity, for instance the moulting success m^z, were a function of the density of all ticks, or some stage of, one would use its value at the relevant equilibrium. In the future, we plan to use models of this structure to complement observational and experimental work on tick-borne infections in the region of Trentino, Italy. Certainly, many parameters of this model have not yet been measured experimentally, so that mainly qualitative trends can be gained by this modelling effort. One of the factors missing in this model, which has instead a profound effect on infection transmission is seasonality (see for instance Randolph *et al.*, 1999); we shall introduce seasonality in the model, although probably explicit expressions will no longer be computable.

4.5 Appendices

APPENDIX A – Stability of tick-free equilibrium

System (7) has a tick-free equilibrium $L=N_i=N_s=A_i=A_s=H_{1i}=H_{1r}=0; \; H_{1s}=H_1>0$. In the linearization of (7) at the tick-free equilibrium, the equations for tick dynamics decouple from those for infection transmission, so that the linearized equations essentially become:

$$\begin{cases} \dfrac{dL}{dt} = g^A(H_1,H_2)a_T(0)A - b_T L - g^L(H_1,H_2)L \\[2mm] \dfrac{dN}{dt} = m^L g^L(H_1,H_2)L - b_T N - g^N(H_1,H_2)N \\[2mm] \dfrac{dA}{dt} = m^N g^N(H_1,H_2)N - b_T A - g^A(H_1,H_2)A. \end{cases} \qquad (A1)$$

which can be written, using matrix notation, as:

$$\frac{d}{dt}\begin{pmatrix} L \\ N \\ A \end{pmatrix} = A_{11}\begin{pmatrix} L \\ N \\ A \end{pmatrix},$$

where

$$A_{11} = \begin{pmatrix} -b_T - g^L(H_1,H_2) & 0 & a_T(0)g^A(H_1,H_2) \\ m^L g^L(H_1,H_2) & -b_T - g^N(H_1,H_2) & 0 \\ 0 & m^N g^N(H_1,H_2) & -b_T - g^A(H_1,H_2) \end{pmatrix}.$$

Formally, this follows from the fact that the Jacobian of (7) at the tick-free equilibrium can be written in the following form:

$$J = \begin{pmatrix} A_{11}^{3x3} & A_{12}^{3x5} \\ 0^{5x3} & A_{22}^{5x5} \end{pmatrix}, \qquad (A2)$$

where

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$$A_{22} = \begin{pmatrix} -b_T - g^N & 0 & 0 & 0 & 0 \\ m^N g^N & -b_T - g^A & 0 & 0 & 0 \\ q^N \beta_1^N H_1^* \psi^N & q^A \beta_1^A H_1^* \psi^A & -(\gamma + b_1 + \alpha) & 0 & 0 \\ 0 & 0 & \gamma & -b_1 & 0 \\ -q^N \beta_1^N H_1^* \psi^N & -q^A \beta_1^A H_1^* \psi^A & a_1'(H_1^*) + a_1(H_I^*) & a_1'(H_1^*) + a_1(H_I^*) & a_1'(H_1^*) + a_1(H_I^*) - b_1 \end{pmatrix}$$

From (A2), we see that the eigenvalues of J are the eigenvalues of A_{11} and of A_{22}. Since A_{22} is triangular, its eigenvalues are the terms on the diagonal, which are all negative, since at equilibrium $a_1(H_I^*) = b_1$ and $a_1(H_I)$ is a decreasing function. Then the study of the local stability of the tick-free equilibrium reduces to the study of (A1).

In order to see whether all the eigenvalues of a matrix have a negative real part, we apply here (and in the other cases) the following theorem, that is a special case of Theorem 6.13 in Diekmann and Heesterbeek (2000).

Theorem A.1. *Let T be a non negative matrix and D a positive diagonal matrix. Let r denote the spectral bound of the matrix T-D and let R_0 the dominant eigenvalue of the positive matrix $K = TD^{-1}$. Then $r < 0 \Leftrightarrow R_0 < 1$.*

We split the matrix A_{11} in the form $A_{11} = T - D$ with T and D respectively:

$$T = \begin{pmatrix} 0 & 0 & a_T(0) g^A(H_1, H_2) \\ m^L g^L(H_I, H_2) & 0 & 0 \\ 0 & m^N g^N(H_I, H_2) & 0 \end{pmatrix},$$

$$D = diag \begin{pmatrix} b_T + g^L(H_1, H_2) \\ b_T + g^N(H_1, H_2) \\ b_T + g^A(H_1, H_2) \end{pmatrix}.$$

Now, we compute the eigenvalues of the matrix TD^{-1} that assumes the following form:

$$TD^{-1} = \begin{pmatrix} 0 & 0 & a_T(0)\dfrac{g^A(H_1,H_2)}{b_T + g^A(H_1,H_2)} \\[3ex] \dfrac{m^L g^L(H_1,H_2)}{b_T + g^L(H_1,H_2)} & 0 & 0 \\[3ex] 0 & \dfrac{m^N g^N(H_1,H_2)}{b_T + g^N(H_1,H_2)} & 0 \end{pmatrix}. \tag{A3}$$

As the hypotheses of Theorem A.1. are satisfied, the stability condition for the tick-free equilibrium is that the spectral radius of TD^{-1} is less than 1. The solutions of the characteristic equation of ($A3$) are the three cubic roots of

$$R_0^{ticks} = a_T(0) \cdot \frac{m^L g^L(H_1,H_2)}{b_T + g^L(H_1,H_2)} \cdot \frac{m^N g^N(H_1,H_2)}{b_T + g^N(H_1,H_2)} \cdot \frac{g^A(H_1,H_2)}{b_T + g^A(H_1,H_2)}.$$

It is clear that they are in module larger than one if and only if $R_0^{ticks} > 1$. Note that, using the definition of Diekmann and Heesterbeek (2000) one would define the basic reproduction number as $\sqrt[3]{R_0^{ticks}}$, which obviously gives the same threshold; we believe that the condition $R_0^{ticks} > 1$ is much easier to interpret.

APPENDIX B – Stability of disease-free equilibrium with only viraemic transmission

When $R_0^{ticks} > 1$ system (7) has a disease-free equilibrium with $N_i = A_i = H_{1i} = H_{1r} = 0$ and the other components at some positive value. In this case too, in the linearization of (7) at the disease-free equilibrium, the equations for tick dynamics decouple from those for infection transmission; the linearized equations for the infected compartments are:

$$\begin{cases} \dfrac{dN_i}{dt} = m^L p^L \beta_1^L H_{1i} \psi^L (H_1, H_2) L - [b_T + g^N (H_1, H_2)] N_i \\[2mm] \dfrac{dA_i}{dt} = m^N p^N \beta_1^N H_{1i} \psi^N (H_1, H_2) N + m^N g^N (H_1, H_2) N_i - [b_T + g^A (H_1, H_2)] A_i) \\[2mm] \dfrac{dH_{1i}}{dt} = q^N \beta_1^N H_1 \psi^N (H_1, H_2) N_i + q^A \beta_1^A H_1 \psi^A (H_1, H_2) A_i - (\gamma + b_1 + \alpha) H_{1i} \end{cases}$$

which can be written, using matrix notation, as:

$$\frac{d}{dt} \begin{pmatrix} N_i \\ A_i \\ H_{1i} \end{pmatrix} = A \begin{pmatrix} N_i \\ A_i \\ H_{1i} \end{pmatrix} \text{, where}$$

$$A = \begin{pmatrix} -b_T - g^N (H_1, H_2) & 0 & m^L p^L \beta_1^L \psi^L (H_1, H_2) L \\ m^N g^N (H_1, H_2) & -b_T - g^A (H_1, H_2) & m^N p^N \beta_1^N \psi^N (H_1, H_2) N \\ q^N \beta_1^N H_1 \psi^N (H_1, H_2) & q^A \beta_1^A H_1 \psi^A (H_1, H_2) & -(b_1 + \gamma + \alpha) \end{pmatrix}.$$

In fact, the Jacobian at the disease-free equilibrium can again be written in the form (A2) (see Appendix A), so that we need only to find the sign of the eigenvalues of A_{11} and of A_{22}. First, we study the sign of the eigenvalues of the block A_{11} that in this case assumes the following form:

$$A_{11} = \begin{pmatrix} a'_T (T^*) A^* g^A - (b_T + g^L) & a'_T (T^*) A^* g^A & a'_T (T^*) A^* g^A + g^A a_T (T^*) \\ m^L g^L & -b_T - g^N & 0 \\ 0 & m^N g^N & -b_T - g^A \end{pmatrix}$$

Using the Routh-Hurwitz criterion we have that the eigenvalues of A_{11} are negative if the following three conditions are satisfied:

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(i) $tr\, A_{11} < 0$

(ii) $det\, A_{11} < 0$

(iii) $M^* \cdot tr\, A_{11} - det\, A_{11} < 0$

where M^* is the sum of the minors of A_{11}.

As $a(T)$ is a decreasing function the condition (i) is trivially satisfied. Using the conditions

at the equilibrium for L^*, N^* and A^* we obtain the following identity:

$$m^L m^N g^L g^N g^A a_T(T^*) = (b_T + g^L)\,(b_T + g^N)\,(b_T + g^A),$$

from which is easy to see that the determinant of A_{11} is always negative (condition *(ii)*).

Finally, it is not difficult to show that also the condition *(iii)* is always satisfied; thus the

eigenvalues of A_{11} have all negative real part.

As for the matrix A_{22}, it can be written as

$$A_{22} = \begin{pmatrix} A^{3x3} & 0^{3x2} \\ \\ B^{2x3} & C^{2x2} \end{pmatrix},$$ (B1)

where $C = \begin{pmatrix} -b_1 & 0 \\ a'_1\,(H_I^*) + a_1\,(H_I^*) & a'_1\,(H_I^*) + a_1\,(H_I^*) - b_1 \end{pmatrix}$

is a triangular matrix with both negative eigenvalues, since at equilibrium $a_1\,(H_I^*) = b_1$.

Then the study of the local stability of the disease-free equilibrium reduces to the study of

the sign of the eigenvalues of the matrix A.

Also in this case, the hypotheses of the Theorem A.1 (see Appendix A) are satisfied;

hence, using the same procedure as for the tick-free equilibrium (Appendix A), we split the

matrix A in the form $A=T-D$, where TD^{-1} is:

$$TD^{-1} = \begin{pmatrix} 0 & 0 & \dfrac{m^L p^L \beta_1^L \psi^L (H_1, H_2) L}{(b_1 + \gamma + \alpha)} \\[3mm] \dfrac{m^N g^N (H_1, H_2)}{(b_T + g^N (H_1, H_2))} & 0 & \dfrac{m^N p^N \beta_1^N \psi^N (H_1, H_2) N}{(b_1 + \gamma + \alpha)} \\[3mm] \dfrac{q^N \beta_1^N H_1 \psi^N (H_1, H_2)}{(b_T + g^N (H_1, H_2))} & \dfrac{q^A \beta_1^A H_1 \psi^A (H_1, H_2)}{(b_T + g^A (H_1, H_2))} & 0 \end{pmatrix} . \qquad (B2)$$

The characteristic equation of (B2) is:

$$f(\lambda) = -\lambda^3 + \lambda \left(\frac{m^L p^L \beta_1^L \psi^L (H_1, H_2) L}{(b_1 + \gamma + \alpha)} \frac{q^N \beta_1^N H_1 \psi^N (H_1, H_2)}{(b_T + g^N (H_1, H_2))} + \frac{m^N p^N \beta_1^N \psi^N (H_1, H_2) N}{(b_1 + \gamma + \alpha)} \frac{q^A \beta_1^A H_1 \psi^A (H_1, H_2)}{(b_T + g^A (H_1, H_2))} \right) +$$

$$+ \frac{m^L p^L \beta_1^L \psi^L (H_1, H_2) L}{(b_1 + \gamma + \alpha)} \frac{m^N g^N (H_1, H_2)}{(b_T + g^N (H_1, H_2))} \frac{q^A \beta_1^A H_1 \psi^A (H_1, H_2)}{(b_T + g^A (H_1, H_2))} = 0$$

From the signs of the coefficients of the cubic, one easily sees that the dominant eigenvalue of TD^{-1} is larger than 1 if and only if $f(1)>0$, that is:

$$\frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{m^N g^N}{b_T + g^N} \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} + \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N} + \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} > 1$$

The LHS of this expression is equal to R_0^{vir} as defined in (9). Hence the stability condition can be stated as $R_0^{vir} < 1$.

Appendix C – Stability of disease-free equilibrium with non-viraemic transmission

In the case with non-viraemic transmission we have that all the blocks of the matrix J are the same of those in the case with only viraemic transmission (Appendix B) except for A_{12} and A_{22} which contain the non-viraemic terms. For the same reasons as in Appendix B, the study of the stability of the disease-free equilibrium reduces to the study of the sign of the eigenvalues of the matrix A that in this case assumes the following form:

$$
A = \begin{pmatrix}
-b_T - g^N + m^L\,\beta_2^L c_2^N \lambda_{NL} LH_2\psi^L\psi^N\!\left(1+\dfrac{\rho_{NL}}{\sqrt{k^L k^N}}\right) & m^L\,\beta_2^L c_2^N \lambda_{NL} LH_2\psi^A\psi^L\!\left(1+\dfrac{\rho_{AL}}{\sqrt{k^A k^L}}\right) & m^L p^L \beta_1^L \psi^L L \\[2ex]
m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2[\psi^N]^2\!\left(1+\dfrac{1}{k}\right) & -b_T - g^A + m^N\,\beta_2^N c_2^A \lambda_{AN} NH_2\psi^A\psi^N\!\left(1+\dfrac{\rho_{AN}}{\sqrt{k^A k^N}}\right) & m^N p^N \beta_1^N \psi^N N \\[2ex]
q^N \beta_1^N H_1\psi^N & q^A \beta_1^A H_1\psi^A & -(b_1+\gamma+\alpha)
\end{pmatrix}.
$$

Splitting the matrix A in the form $A=T\text{-}D$, as in the Appendix B, we choose

$$
T = \begin{pmatrix}
0 & m^L\,\beta_2^L c_2^N \lambda_{NL} LH_2\psi^A\psi^L(1+\rho_{AL}/\sqrt{k^A k^L}) & m^L p^L \beta_1^L \psi^L L \\[2ex]
m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2[\psi^N]^2(1+1/k^N) & 0 & m^N p^N \beta_1^N \psi^N N \\[2ex]
q^N \beta_1^N H_1\psi^N & q^A \beta_1^A H_1\psi^A & 0
\end{pmatrix}
$$

and

$$
D = diag\begin{pmatrix}
b_T + g^N - m^L\,\beta_2^L c_2^N \lambda_{NL} LH_2\psi^L\psi^N(1+\rho_{NL}/\sqrt{k^L k^N}) \\[2ex]
b_T + g^A - m^N\,\beta_2^N c_2^A \lambda_{AN} NH_2\psi^A\psi^N(1+\rho_{AN}/\sqrt{k^A k^N}) \\[2ex]
b_1 + \gamma + \alpha
\end{pmatrix}.
$$

In this case the hypothesis of the Theorem A.1 (see Appendix A) are not always satisfied: in fact, the elements of D may not be positive. Therefore, before computing the eigenvalues of the matrix TD^{-1} as in the case with only viraemic transmission, we must consider the cases when the elements of D are not positive. Note that it would be possible to split the matrix A in a form $A=T\text{-}D$ in such a way that the diagonal D is strictly positive. Indeed, this is required in the definition of R_0 given by Diekmann and Heesterbeek (2000)

who also suggest the use of a transition matrix Σ, writing $A=T+\Sigma–D$; however, the computations appear much simpler using the present form.

Using results of loop analysis (Puccia and Levins, 1985), we study the stability of the disease-free equilibrium when the diagonal elements of the matrix A are not negative.

To do that, we apply the stability criteria based on the loop model notation (Puccia and Levins, 1985), to the matrix A.

The following three cases have to be considered:

 - Case1. The first two diagonal elements of A are positive ($a_{11}, a_{22}>0$) while the third is negative

($-a_{33}<0$). In this case the feedback at level 1 and 2 (Puccia and Levins, 1985) become:

$F_1=a_{11}+a_{22}-a_{33}$

$F_2=a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}-a_{11}a_{22}+a_{11}a_{33}+a_{22}a_{33.}$

The stability condition at level 1, $F_1<0$, (Puccia and Levins, 1985), implies that $a_{33}>a_{11}+a_{22}$. Inserting this inequality in the feedback at level 2 we obtain:

$F_2>a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}--a_{11}a_{22}+a_{11}(a_{11}+a_{22})+a_{22}a_{33}=a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+(a_{11})^2{}_{+}a_{22}a_{33}>0.$

Thus, the stability condition at level 2, $F_2<0$, (Puccia and Levins, 1985), is not met and the equilibrium is unstable.

 - Case2. The first diagonal element of A is positive ($a_{11}>0$) while the second and third are negative ($-a_{22}, -a_{33}<0$). In this case the feedback are:

$F_1=a_{11}-a_{22}-a_{33}$

$F_2=a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}+a_{11}a_{33}-a_{22}a_{33.}$

$F_3=a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}-a_{11}a_{23}a_{32}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}+a_{11}a_{22}a_{33}.$

The stability condition al level 2, $F_2<0$, implies that:

$a_{22}a_{33}>a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}+a_{11}a_{33}.$

Inserting this inequality in the feedback at level 3 we obtain:

$F_3>a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}+$

$-a_{11}a_{23}a_{32}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}+a_{11}(a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}+a_{11}a_{33})=$

$=a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}+a_{11}a_{12}a_{21}+a_{11}a_{13}a_{31}+(a_{11})^2(a_{11}+a_{22})>0.$

Thus the stability condition at level 3, $F_3<0$, (Puccia and Levins, 1985), is not met and the equilibrium is unstable.

 - Case3. The second diagonal element of A is positive ($a_{22}>0$) while the first and third are negative ($-a_{11}, -a_{33}<0$). In this case feedback assume the following form:

$F_1=a_{22}-a_{11}-a_{33}$

$F_2=a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}-a_{11}a_{33}+a_{22}a_{33.}$

$F_3=a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}+a_{11}a_{23}a_{32}-a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}+a_{11}a_{22}a_{33}.$

The stability condition al level 2, $F_2<0$, implies that:
$a_{11}a_{33}>a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}+a_{22}a_{33}.$

Inserting this inequality in the feedback at level 3 we obtain:

$F_3>a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}+a_{11}a_{23}a_{32}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21+}$

$+a_{22}(a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+a_{11}a_{22}+a_{22}a_{33})=$

$=a_{12}a_{23}a_{32}+a_{21}a_{32}a_{13}+a_{11}a_{23}a_{32}+a_{22}a_{12}a_{21}+a_{22}a_{23}a_{32}+(a_{22})^2(a_{11}+a_{33})>0.$

Thus the stability condition at level 3 is not met and the equilibrium is unstable. We conclude that in all three cases the disease-free equilibrium is unstable.

We now consider the case where the hypotheses of Theorem A.1 are satisfied; then the matrix TD^{-1} assume the following form, where all the denominators are strictly positive:

$$TD^{-1} = \begin{pmatrix} 0 & \dfrac{m^L \beta_2^L c_2^A \lambda_{AL} LH_2 \psi^A \psi^L (1+\rho_{AL}/\sqrt{k^A k^L})}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N (1+\rho_{AN}/\sqrt{k^A k^N})} & \dfrac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \\[2em] \dfrac{m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2 [\psi^N]^2 (1+1/k^N)}{b_T + g^N - \beta_2^L c_2^N \lambda_{NL} m^L LH_2 \psi^N \psi^L (1+\rho_{NL}/\sqrt{k^N k^L})} & 0 & \dfrac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \\[2em] \dfrac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N - m^L \beta_2^L c_2^N \lambda_{NL} LH_2 \psi^N \psi^L (1+\rho_{NL}/\sqrt{k^N k^L})} & \dfrac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N (1+\rho_{AN}/\sqrt{k^A k^N})} & 0 \end{pmatrix}$$

From Theorem A.1 (Appendix A) we get that, in the case with non-viraemic transmission, the threshold condition for disease extinction is, given the positivity of the matrix D, the following:

$$R_0^{all} = \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \cdot \frac{m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2 [\psi^N]^2 \left(1+\frac{1}{k^N}\right)}{b_T + g^N - m^L \beta_2^L c_2^N \lambda_{NL} LH_2 \psi^N \psi^L \left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right)} \cdot \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N \left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right)} +$$

$$+ \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \cdot \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N - m^L \beta_2^L c_2^N \lambda_{NL} LH_2 \psi^N \psi^L \left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right)} +$$

$$+ \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \cdot \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N \left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right)} +$$

$$+ \frac{m^N g^N + m^N \beta_2^N c_2^N \lambda_{NN} NH_2 [\psi^N]^2 \left(1+\frac{1}{k^N}\right)}{b_T + g^N - m^L \beta_2^L c_2^N \lambda_{NL} LH_2 \psi^N \psi^L \left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right)} \cdot \frac{m^L \beta_2^L c_2^A \lambda_{AL} LH_2 \psi^A \psi^L \left(1+\frac{\rho_{AL}}{\sqrt{k^A k^L}}\right)}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N \left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right)} +$$

$$+ \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \cdot \frac{m^L \beta_2^L c_2^A \lambda_{AL} LH_2 \psi^A \psi^L \left(1+\frac{\rho_{AL}}{\sqrt{k^A k^L}}\right)}{b_T + g^A - m^N \beta_2^N c_2^A \lambda_{AN} NH_2 \psi^A \psi^N \left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right)} \cdot \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N - m^L \beta_2^L c_2^N \lambda_{NL} LH_2 \psi^N \psi^L \left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right)} < 1.$$

By some very simple algebra, it can be seen that this expression is identical to that shown in (12) to make the biological interpretation more transparent.

Conversely, the disease-free equilibrium will be unstable, and the disease will persist, if D is not positive or $R_0^{all} > 1$.

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Chapter 5

Modelling the Dynamics of Lyme Disease and Tick-Borne Encephalitis in Trentino (Northern Italy)

Manuscript

by

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5.0 Abstract

Lyme disease and Tick-Borne Encephalitis (TBE) are two emerging tick-borne diseases in Trentino (northern Italy) transmitted by the pan-european tick *Ixodes ricinus*. Rodents act both as reservoirs for pathogens and as hosts for ticks, while large herbivores such as the roe-deer, serve principally as hosts for ticks.

Starting from a general model framework for tick-borne infections we apply the model to two specific systems and explore the dynamics of Lyme disease and TBE in Trentino. We show numerical results, using parameter estimates based on a detailed field study and explore the effects of uncertainty on the endemic equilibrium of both models. Models also provide an explicit formula for the thresholds for ticks and disease persistence assuming only viraemic transmission for Lyme disease while for TBE we permit only transmission through co-feeding ticks. We use joint threshold host density curves to illustrate the persistence of ticks and disease in both cases. With the parameter chosen for Lyme disease the 'dilution effect' due to the increase of roe deer does not occur while for TBE both an increase of deer and rodent density might act against the persistence of the virus.

5.1 Introduction

Tick-borne infections are caused by pathogens transmitted between hosts by ticks that become infected with the pathogen following a blood meal. Among the zoonotic tick-borne diseases, Rickettsiosis, Lyme Disease, Ehrlichiosis and TBE (tick-borne encephalitis) are emerging as international human health treat (Hudson *et al.*, 2002).

Trentino province, a mountainous region in the north-eastern part of the Italian Alps, is inhabited by the tick *Ixodes ricinus* and the area is now recognised as an endemic area for Lyme disease, TBE and Rickettsiosis (Hudson *et al.*, 2001; Rizzoli *et al.*, 2002; Beninati *et al.*, 2003). For TBE, this is at the very southern end of its range and where the

disease is thought to occur in a series of discrete pockets. These diseases have caused some concern and as a consequence a number of mathematical models have been produced to explore the dynamics and specific means of preventing infection of humans. Some workers have used complex models mainly based on theoretical computer simulations (see Van Buskirk and Ostfeld, 1995), while simpler models, based on differential equations, have been developed by O'Callaghan *et al.* (1997), Caraco *et al.* (1998), Norman *et al.* (1999), Rosà *et al.* (2003).

One of the advantages in using these simpler models is that it is possible to estimate the basic reproduction number thus allowing the understanding of the condition which permit to a pathogens to persist. In their simplicity, these models are however rather complex, so it is difficult to study analytically their behaviour, or even the nontrivial equilibria, above the threshold for persistence. Therefore, here we study numerically, using realistic parameter values for Lyme borreliosis and Tick-Borne Encephalitis in Trentino, how the endemic equilibrium and the basic reproduction number for both the diseases change with some parameters.

5.2 Models

The two models considered here are both special cases of the general model for tick-borne infections presented in Rosà *et al.* (2003) to which we send for more details. Tick's life cycle include three developmental stages (larvae, nymphs and adults) whose densities will be denoted here *L*, *N* and *A*, that feed on one, two or three hosts depending upon the species: we will only consider the three-host case.

5.2.1 Lyme Disease

Lyme disease, described by Steere *et al.* (1977), following a mysterious outbreak of arthritis in children who lived near Lyme, Connecticut, is an infectious disease that affects the skin first, then the joints, the nervous system and, if untreated, eventually other organs.

It is caused by a bacterial spirochaete, *Borrelia burgdorferi* s.l. (Burgdorfer *et al*., 1982) that is transmitted by infected ticks belonging to the *Ixodes ricinus* complex.

This is a multi-species system involving the bacterium *Borrelia burgdorferi* s.l., the ticks which carry the bacteria and different hosts (rodents and deer in particular) that are fed on by ticks. Some hosts, especially rodents, act as reservoirs of the infection, meaning that they can acquire the pathogen by infected ticks and transmit it to other ticks. Other hosts, such as deer, are classified as tick maintenance host and they simply amplify the tick population without amplifying the pathogen. Ticks can also transmit the infection to humans which are an occasional host .

For Lyme disease, the main route of transmission is from infected tick to a susceptible host and vice versa: this type of transmission is often denoted viraemic transmission (even though in this case should be denoted as bacteriemic transmission). Recently it has been discovered (Gern and Rais, 1996) that pathogens can be transmitted from an infected tick to a non-infected tick while they *co-feed* on the same host: this process is known as non-viraemic transmission, but, for the sake of simplicity, this route of transmission will not be considered in our model for Lyme Disease.

In the model considered here, nymphs and adult ticks are divided into infected and susceptible classes. It is assumed that ticks feed on two host species (for instance rodents and roe deer). Hosts of type 1 (whose size is denoted as H_1) can become infected and transmit the infection, then they are divided into three classes, namely susceptible (H_{1s}), infected (H_{1i}) and immune(H_{1r}). Hosts of type 2 (whose size is assumed to be a constant H_2) can not transmit the infection, and is relevant only in so far as it sustains the tick population.

The equations of the model are the following:

$$\begin{cases}
\dfrac{dL}{dt} = g^A(H_1, H_2) a_T(T)(A_i + A_s) - d_T L - g^L(H_1, H_2)L \\[2mm]
\dfrac{dN_s}{dt} = m^L g^L(H_1, H_2)L - m^L \beta_1^L H_{1i} \psi^L(H_1, H_2)L - d_T N_s - g^N(H_1, H_2)N_s \\[2mm]
\dfrac{dN_i}{dt} = m^L \beta_1^L H_{1i} \psi^L(H_1, H_2)L - d_T N_i - g^N(H_1, H_2)N_i \\[2mm]
\dfrac{dA_s}{dt} = m^N g^N(H_1, H_2)N_s - m^N \beta_1^N H_{1i} \psi^N(H_1, H_2)N_s - d_T A_s - g^A(H_1, H_2)A_s \\[2mm]
\dfrac{dA_i}{dt} = m^N \beta_1^N H_{1i} \psi^N(H_1, H_2)N_s + m^N g^N(H_1, H_2)N_i - d_T A_i - g^A(H_1, H_2)A_i \\[2mm]
\dfrac{dH_{1s}}{dt} = a_1(H_1)H_1 - d_1 H_{1s} - q^N \beta_1^N H_{1s} \psi^N(H_1, H_2)N_i - q^A \beta_1^A H_{1s} \psi^A(H_1, H_2)A_i \\[2mm]
\dfrac{dH_{1i}}{dt} = q^N \beta_1^N H_{1s} \psi^N(H_1, H_2)N_i + q^A \beta_1^A H_{1s} \psi^A(H_1, H_2)A_i - (d_1 + \gamma + \alpha)H_{1i} \\[2mm]
\dfrac{dH_{1r}}{dt} = \gamma H_{1i} - d_1 H_{1r}
\end{cases} \qquad (1)$$

All the parameters of the model and their biological interpretation are listed in Table 1. The function g^z describes the rate at which ticks in stage z encounter hosts, considering the extended feeding period (Mwambi *et al.*, 2000), while ψ^z are auxiliary functions; their expressions are the following:

$$\psi^z(H_1, H_2) = 1/(1 + c_1^z H_1 + c_2^z H_2) \text{ and } g^z(H_1, H_2) = (\beta_1^z H_1 + \beta_2^z H_2)/1 + c_1^z H_1 + c_2^z H_2,$$

where $c_j^z = \beta_j^z / \sigma$ for $z = L, N, A$ and $j = 1, 2$.

Density-dependence is assumed, for the sake of simplicity, to occur only in two quantities: the production of larvae per feeding adult tick $a_T(T)$ and the birth rate for host $a_1(H_1)$. Note however that there is some evidence for density-dependence in all moulting probabilities (Randolph and Rogers, 1997). As for the functional form of density dependence, we chose the simplest:

$$a_T(T) = r_T - s_T T \text{ and } a_1(H_1) = r_1 - (r_1 - d_1)/K_1, \qquad (2)$$

where r_1 and d_1 are the natural birth and death rate of hosts 1, and K_1 is their carrying capacity; r_T is the average egg production per fed adult tick, and s_T is related to ticks' carrying capacity.

The basic reproduction number for ticks is given by the following expression (Rosà *et al.*, 2003):

$$R_{0,ticks} = a_T(0) \frac{m^L g^L(H_1, H_2)}{d_T + g^L(H_1, H_2)} \frac{m^N g^N(H_1, H_2)}{d_T + g^N(H_1, H_2)} \frac{g^A(H_1, H_2)}{d_T + g^A(H_1, H_2)}. \tag{3}$$

This quantity represents the threshold condition for the persistence of ticks in the system. When $R_{0,ticks} > 1$ the ticks will persist and, from numerical simulation, it appears that tick and host populations will settle to a positive coexistence equilibrium. In general, and as observed in our filed observation, adult ticks do not feed on rodents (H_1 in this case) then we have $\beta_1^A = 0$ and the formula for the basic reproduction number for the disease found in Rosà *et al.* (2003), in the case of only viraemic transmission, assumes the following form:

$$R_{0,Lyme} = \frac{m^L \beta_1^L \psi^L L}{d_1 + \gamma + \alpha} \cdot \frac{q^N \beta_1^N H_1 \psi^N}{d_T + g^N}, \tag{4}$$

where all quantities L, N, A and H_1 are computed at the pathogen-free equilibrium. Recall that $R_{0,Lyme} > 1$ is the condition for pathogen persistence.

5.2.2 Tick-Borne Encephalitis

Tick-borne Encephalitis (TBE) is caused by a virus of a distinct antigenic complex of the Flaviviridae that includes Louping ill, Kysanur forest disease, Omsk haemorrhagic disease, and Powassan virus (Randolph *et al.*, 2002). Western tick-borne Encephalitis (TBE) is a zoonosis of significance in many parts of Europe. Although several tick species are competent vectors, natural ecological constraints make *Ixodes ricinus* the only significant vector in the wild (Labuda and Randolph, 1999). Among different transmission routes the most efficient one seems to be the saliva-activated non-viraemic transmission

between co-feeding ticks (transmission between ticks feeding together on the same host). In fact, many workers have demonstrated that certain tick hosts, rodents in particular, which do not produce a viraemic response will permit non-viraemic transmission between co-feeding ticks (Jones *et al.*, 1987; Labuda *et al.*, 1993). Randolph *et al.* (1996, 1999) have shown the importance of co-feeding and temporal coincidence of different tick stages in the maintenance of TBE. As viraemic transmission seems to be less important than the transmission trough co-feeding, in our model for TBE we assume that the only route of transmission is the non-viraemic transmission. This means that there are no competent hosts in the system and the reservoir of the diseases are exclusively the ticks. Also in this case it is assumed that ticks feed on two host species, but here both hosts are assumed to be at constant size. H_1 (for instance roe deer) is relevant only in sustaining the tick population, while on H_2, for instance rodents, the co-feeding transmission between ticks might occur. The equations of the model are the following:

$$
\begin{cases}
\dfrac{dL}{dt} = g^A(H_1,H_2)a_T(T)(A_i+A_s) - d_T L - g^L(H_1,H_2)L \\[2mm]
\dfrac{dN_s}{dt} = m^L g^L(H_1,H_2)L - d_T N_s - g^N(H_1,H_2)N_s - m^L \beta_2^L L H_2 \psi^L(H_1,H_2) + \\
\qquad - m^L \beta_2^L L H_2 \psi^L(H_1,H_2)[1-\exp\{-\lambda_{NL}c_2^N N_i \psi^N(H_1,H_2)(1+\rho_{NL}/\sqrt{k^N k^L})\}] + \\
\qquad - m^L \beta_2^L L H_2 \psi^L(H_1,H_2)[1-\exp\{-\lambda_{AL}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{ANL}/\sqrt{k^A k^L})\}] \\[2mm]
\dfrac{dA_s}{dt} = m^N g^N(H_1,H_2)N_s - d_T A_s - g^A(H_1,H_2)A_s + \\
\qquad - m^N \beta_2^N N_s H_2 \psi^N(H_1,H_2)[1-\exp\{-\lambda_{NN}c_2^N N_i \psi^N(H_1,H_2)(1+1/k^N)\}] + \\
\qquad - m^N \beta_2^N N_s H_2 \psi^N(H_1,H_2)[1-\exp\{-\lambda_{AN}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AN}/\sqrt{k^A k^N})\}] \\[2mm]
\dfrac{dN_i}{dt} = -d_T N_i - g^N(H_1,H_2)N_i + \\
\qquad + m^L \beta_2^L L H_2 \psi^L(H_1,H_2)[1-\exp\{-\lambda_{NL}c_2^N N_i \psi^N(H_1,H_2)(1+\rho_{NL}/\sqrt{k^N k^L})\}] + \\
\qquad + m^L \beta_2^L L H_2 \psi^L(H_1,H_2)[1-\exp\{-\lambda_{AL}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{ANL}/\sqrt{k^A k^L})\}] \\[2mm]
\dfrac{dA_i}{dt} = m^N g^N(H_1,H_2)N_i - d_T A_i - g^A(H_1,H_2)A_i + \\
\qquad + m^N \beta_2^N N_s H_2 \psi^N(H_1,H_2)[1-\exp\{-\lambda_{NN}c_2^N N_i \psi^N(H_1,H_2)(1+1/k^N)\}] + \\
\qquad + m^N \beta_2^N N_s H_2 \psi^N(H_1,H_2)[1-\exp\{-\lambda_{AN}c_2^A A_i \psi^A(H_1,H_2)(1+\rho_{AN}/\sqrt{k^A k^N})\}].
\end{cases}
\tag{5}
$$

All the parameters of the model and their biological interpretation are listed in Table 3. As adult ticks do not feed on rodents (H_2 in this case) we have $\beta_2^A = 0$. This implies that co-feeding including adults cannot take place on H_2 and it means that $\lambda_{AL} = \lambda_{AN} = 0$. This simplifies the formula for the basic reproduction number for the disease found in Rosà *et al.* (2003) that in this case assumes the following form:

$$R_{0,TBE} = \frac{m^L \lambda_{NL} \beta_2^L c_2^N L H_2 \psi^N \psi^L (1 + \rho_{NL} / \sqrt{k^N k^L})}{d_T + g^N}. \tag{6}$$

Recall that when $R_{0,TBE}$ is greater than 1 the pathogen persists in the system even without hosts that sustain the infection.

5.3 Parameters estimation

5.3.1 Lyme Disease
Our parameter choice has been tuned towards the dynamics of Lyme borreliosis in the province of Trento, Italy, where the relevant tick species is *Ixodes ricinus* while H_1 represent small rodents (especially *Apodemus* spp. and *Clethrionomys glareolus*) and H_2 roe deer.

As far as possible, we used parameter estimates taken from the literature or derived from data collected by researchers of the Centre for Alpine Ecology (CEA); however, for some parameters we could produce only educated guesses. All the parameter values used are listed in Tables 1 and 2 where we measure time in days and densities in hectare^{-1} (ha^{-1}).

Concerning ticks' demographic parameters, adult female are assumed to produce around 3000 eggs per each (Randolph and Rogers, 1997) so r_T is taken as 1300 that is around half of this values because in our model adults include both male and female ticks. The mortality of ticks d_T is taken 0.02 days^{-1}, it means that ticks could survive a couple of months on the vegetation without finding a host (Randolph and Rogers, 1997). As we

assumed that the production of larvae per feeding adult tick $a_T(T)$ is density-dependent we set s_T, in equation (2), equal to 0.73 in order to find at the equilibrium a total density of ticks around 1500 per hectare (roughly the value we obtained from the data).

TABLE 1. Notation and values for variables and parameters included in the model for Lyme Disease.

Symbol	Description	Value (units)
L	Larval density	variable (ha^{-1})
N_i	Infected nymph density	variable (ha^{-1})
N_s	Susceptible nymph density	variable (ha^{-1})
A_i	Infected adult density	variable (ha^{-1})
A_s	Susceptible adult density	variable (ha^{-1})
T	Total tick density	$=L+N_i+N_s+A_i+A_s$
r_T	Average egg production per fed adult tick	1300
d_T	Natural death rate of ticks	0.02 (days^{-1})
s_T	Density-dependent death rate of ticks	0.73 (ha)
H_{1s}	Density of susceptible hosts 1	variable (ha^{-1})
H_{1i}	Density of infected hosts 1	variable (ha^{-1})
H_{1r}	Density of immune hosts 1	variable (ha^{-1})
H_1	Total density of viraemic hosts (rodents)	$=H_{1s}+H_{1i}+H_{1r}$
r_1	Natural birth rate of hosts 1	0.014 (days^{-1})
d_1	Natural death rate of hosts 1	0.003 (days^{-1})
K_1	Carrying capacity of hosts1	30 (ha^{-1})
H_2	Non-viraemic host density (roe deer)	0.1 (ha^{-1})
β_i^z	Encounter rate between questing ticks of stage z ($z=L,N,A$) and hosts H_i ($i=1,2$)	see Table 2
σ	Detachment rate of ticks	0.5 (days^{-1})
m^z	Moulting success probability for ticks of stage z ($z=L,N$)	0.15
q^z	Probability of becoming infected for a host 1 bitten by an infected tick in stage z ($z=N,A$)	?
α	Disease related death rate of host 1	? (days^{-1})
γ	Recovery rate of viraemic host	? (days^{-1})

As the detachment rate of ticks σ is given by 1/(feeding time) and this feeding time is 2-3 days, we set σ to 0.5 and, for the sake of simplicity, we choose the same value for all tick stages. The parameters m^L and m^N represent the probability of moulting success for larvae and nymphs after feeding. In practise, m^N may depend on the host species (Humair et al., 1999) so to be accurate we should use different values for host 1 and 2, but for sake of simplicity here we choose the same values for both hosts and we also choose the same value for larvae and nymphs setting $m^L=m^N=0.15$ (Humair et al., 1999). For host 1, in this case rodents, we choose a natural death rate d_1 of 1/365 as the average lifespan for rodents is around one year. Regarding the natural birth rate we choose the average values of 5 offspring per year, setting $r_1=5/365$. Also for host 1 we assume a density-dependence in the birth rate (see eq. (2)) setting the carrying capacity $K_1=30$ by taking an average from the data in Trentino.

From the general model (Rosà et al., 2003), if N is the density of nymphs present in the system, N_{F_1} the nymphs feeding on host 1 while N_Q the questing nymphs, we have that these quantities are in the following quasi-equilibrium relations:

$$N_{F_1} = \frac{c_1^N H_1 N}{1 + c_1^N H_1 + c_2^N H_2} \text{ and } N_Q = \frac{N}{1 + c_1^N H_1 + c_2^N H_2}. \tag{7}$$

From these equations we get

$$\frac{N_{F_1}}{N_Q} = c_1^N H_1 = \frac{\beta_1^N H_1}{\sigma},$$

and it gives the following formula for calculating the encounter rate between nymphs and host 1:

$$\beta_1^N = \sigma \frac{N_{F_1}}{N_Q H_1} \tag{8}$$

In the same way we obtain the encounters rate between larvae and host 1:

$$\beta_1^L = \sigma \frac{L_{F_1}}{L_Q H_1} \, . \tag{9}$$

In Province of Trento, questing ticks were collected by dragging 30 transects of 100 meter located within an endemic focus both for Lyme disease and TBE, between May and September 2000. Tick attached to host, and in particular feeding larvae and nymphs (no adult ticks were found), were collected from 47 mice (*Apodemus* spp.) which were live-trapped in the same area where the questing ticks were collected (unpublished data). Inserting in (8) and (9) these observed data concerning feeding and questing ticks we estimated the encounter rates between rodents and tick stages reported in Tab. 2.

TABLE 2. Notation and values for encounter rates between questing ticks and hosts.

Symbol for Lyme	Symbol for TBE	Description	Value
β_1^L	β_2^L	Encounter rate between questing larvae and rodents	0.028402
β_1^N	β_2^N	Encounter rate between questing nymphs and rodents	0.000887
β_1^A	β_2^A	Encounter rate between questing adults and rodents	0
β_2^L	β_1^L	Encounter rate between questing larvae and roe deer	0.048798
β_2^N	β_1^N	Encounter rate between questing nymphs and roe deer	0.028779
β_2^A	β_1^A	Encounter rate between questing adults and roe deer	0.12849

As it was practically impossible to estimate the encounter rate of the tick with its natural feeder host 2 (roe deer), an experiment with tracer animals (domesticated goats) was carried out obtaining the numerical values reported in Tab. 2. In this experiment we used 5 goats which were let to feed for a standardized period of time (75 minutes) every 15 days between august 1999 and august 2000, for a total of 27 replication. Goats were screened before every walk and ticks counted.

Finally, parameters for which there exist no sensible estimates are q^N, q^A and α which we will vary in the simulation. As for γ, while it is known that infected mice remain positive for a couple of weeks, ($\gamma \approx 1/15$ days^{-1}) it is generally thought that infected mice remain infectious, although perhaps to a lesser degree, forever ($\gamma \approx 0$); thus, we will let also γ vary.

5.3.2 Tick-borne Encephalitis

Also for TBE in Trentino the relevant tick species is *Ixodes ricinus* but in this case the notation for hosts has to be changed; namely, here H_1 represent roe deer and H_2 small rodents (where co-feeding takes place).

TABLE 3. Notation and values for variables and parameters included in the model for Tick-borne Encephalitis.

Symbol	Description	Value
L	Larval density	variable (ha^{-1})
N_i	Infected nymph density	variable (ha^{-1})
N_s	Susceptible nymph density	variable (ha^{-1})
A_i	Infected adult density	variable (ha^{-1})
A_s	Susceptible adult density	variable (ha^{-1})
T	Total tick density	$=L+N_i+N_s+A_i+A_s$
r_T	Average egg production per fed adult tick	1300
d_T	Natural death rate of ticks	0.02 (days^{-1})
s_T	Density-dependent death rate of ticks	0.73 (ha)
H_1	Host 1 density (roe deer)	0.1 (ha^{-1})
H_2	Host 2 density (rodents)	30 (ha^{-1})
β_i^z	Encounter rate between questing ticks of stage z ($z=L,N,A$) and hosts H_i ($i=1,2$)	see Table 2
σ	Detachment rate of ticks	0.5 (days^{-1})
m^z	Moulting success probability for ticks of stage z ($z=L,N$)	0.15
ρ_{NL}	Correlation coefficient for nymphs and larvae	0.43
k^L	Aggregation parameter of the Negative Binomial distribution for larvae	2.1
k^N	Aggregation parameter of the Negative Binomial distribution for nymph	0.42
λ_{LN}	Co-feeding probability between infected nymphs and larvae	?
λ_{NN}	Co-feeding probability between infected and susceptible nymphs	?

All parameters concerning ticks and hosts are the same to those for Lyme Disease while the encounter rates between ticks and host should be exchange as reported in Table 2. All the parameter used for TBE are listed in Table 3.

For TBE the pattern of tick distribution on rodents might play an important role in the transmission through co-feeding (the only route of transmission present in the system). In the model (5) ticks stages are assumed to follow a Negative Binomial distribution. This assumption is well supported by the observed pattern of feeding larvae and nymphs on rodents in Trentino (Fig. 1). In fact, both distribution fit quite well the Negative Binomial distribution and nymphs result strongly aggregated (k^N=0.42) while larvae show a less aggregated distribution (k^L=2.1).
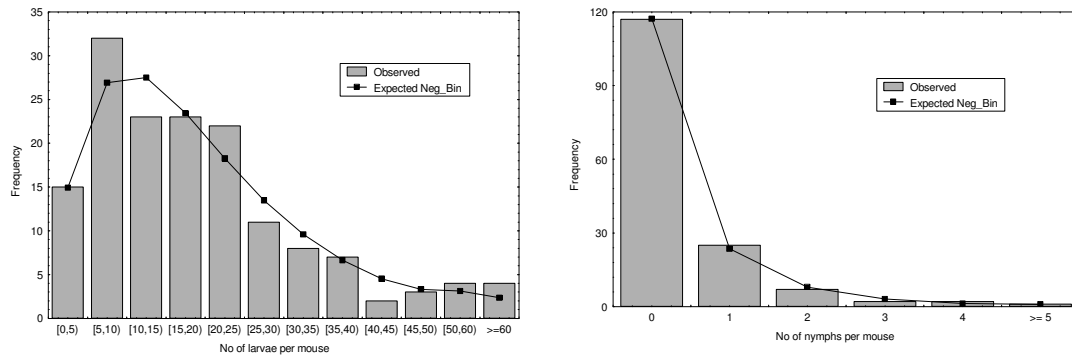

FIG. 1. Observed larvae and nymphs frequency distributions on rodents in Trentino compared with expected distribution based on the Negative Binomial distribution, estimated by maximum likelihood techniques (Negative Binomial fit: for larvae chi-square=29.33, df=27, p=0.34; for nymphs chi-square=1.04, df=3, p=0.79). The k of the Negative Binomial for larvae is k^L=2.1 and for nymphs k^N=0.42.

In addition both distributions result coincident rather than independent. In fact, a linear correlation was found (P<0.01) between feeding larvae and nymphs on rodents and the resulting correlation coefficient ρ_{LN} is equal to 0.43 (Fig. 2).

No sensible estimates exist for the co-feeding probability then we will let λ_{LN} and λ_{NN} vary in the simulations. These parameters include the probability for a tick of being in a co-

feeding group, the probability of being infected in that case and the probability of the infection being maintained trans-stadially.
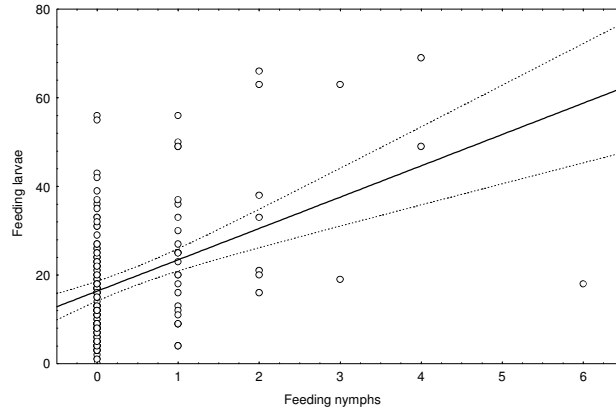

FIG. 2. Linear correlation between feeding nymphs and larvae on rodents in Trentino.

5.4 Simulations

In this Section we show some numerical results, looking in particular at the effect of some parameters on the endemic equilibrium and on the basic reproduction numbers of both models.

5.4.1 Lyme Disease

We let one parameter vary at a time (Fig. 3), while all other parameters are set at the values listed in Tables 1 and 2; for the uncertain ones we start using: $q^N=q^A=0.3$, $\gamma=0.01$, $\alpha=0.005$. For this set of parameters we find a positive equilibrium point at: $L\approx700$, $N_s\approx556$, $N_i\approx137$, $A_s\approx58$, $A_i\approx30$, $H_{1s}\approx2$, $H_{1i}\approx6$, $H_{1r}\approx22$; while the reproduction numbers result $R_{0,ticks}\approx6$ and $R_{0,Lyme}\approx13$. It was found (Rosà *et al.*, 2003) that an increase of H_2 may decrease $R_{0,Lyme}$, hence act against parasite persistence, since, when H_2 is large, many bites of infected ticks get 'wasted' on incompetent hosts: this was named the 'dilution effect'. Here we see (see Fig. 3A) that, for these parameter values, the 'dilution effect' does not occur: as H_2 is increased, the equilibrium value of infected hosts first increases sharply and then stabilizes. A branching point is at H_2 approx. 0.012, meaning that below this value, $R_{0,Lyme} < 1$.

As expected, the density of infected hosts increases with increasing q^N, first sharply, then more moderately. The threshold value is at q^N approx. 0.023 (see Fig. 3B).
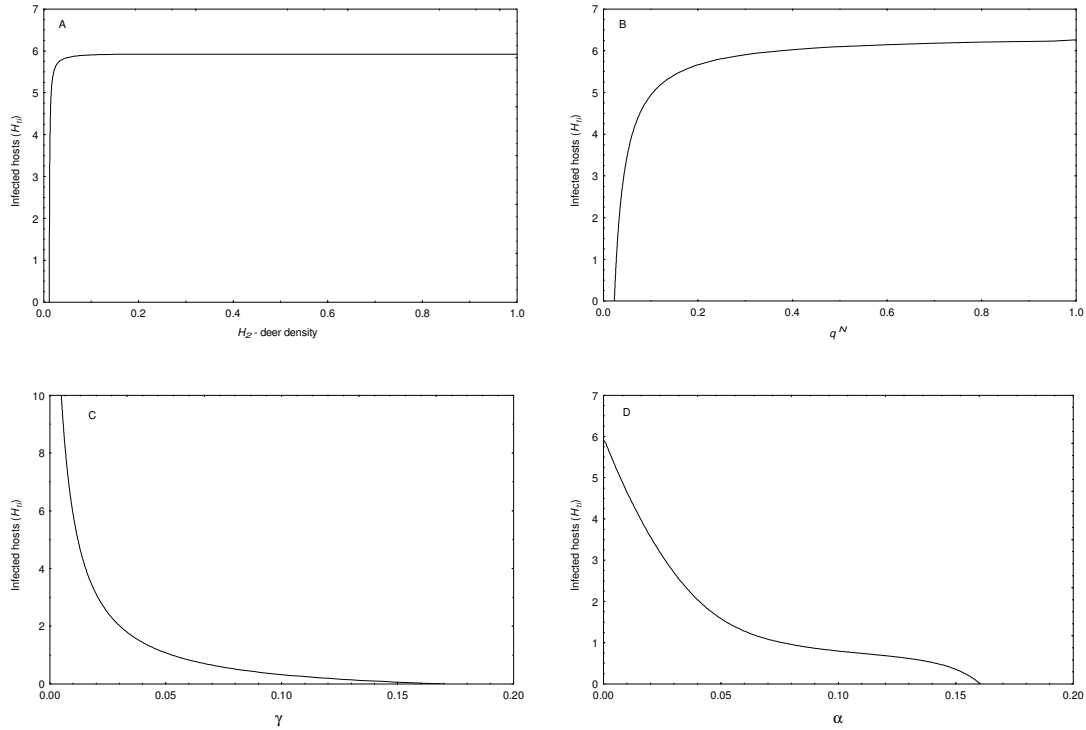

FIG. 3. Variation of the equilibrium level of infected host H_{1i} with H_2 (Fig. A), q^N (Fig. B), γ (Fig.C) and α (Fig. D). The other parameters values are reported in Tables 1 and 2.

With increasing γ, the density of infected hosts decreases (see Fig. 3C) and at γ approx 0.17 we get a branching point. When γ approaches 0, the density of infected hosts greatly increases. Finally, the density of infected hosts decreases monotonically with increasing α (disease-induced death rate of mice) up to the branching point at α approx. 0.16 (Fig. 3D). Setting $R_{0,ticks}$ to 1 and plot H_1 against H_2 using our parameter values (Tables 1 and 2) we can determine the densities of rodents and roe deer that must be present for ticks to persist (Fig. 4). It can be seen that the curve do not cross the rodent axis since in our data adult ticks do not feed on rodents. Hence the ticks cannot persist in the absence of an adult tick host, usually a large mammal, in our case roe deer.

If we take $R_{0,Lyme}$=1 we produce the persistence-extinction boundary that determines the density of viraemic and non-viraemic host that must be present for borrelia to persist (Fig. 5).
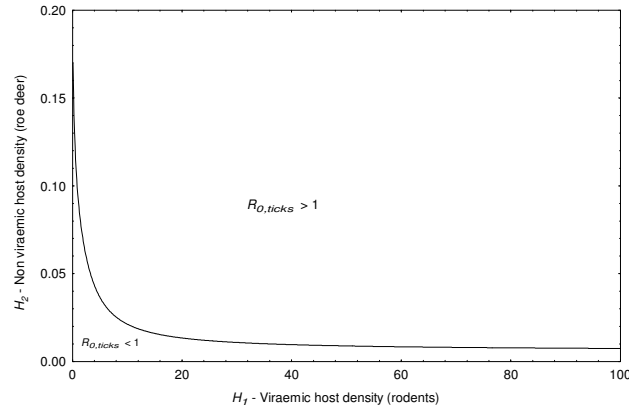

FIG. 4. The effect of hosts densities on $R_{0,ticks}$. The parameter values are those reported in Tables 1 and 2 with $q^N=q^A=0.3$, γ=0.01, α=0.005.
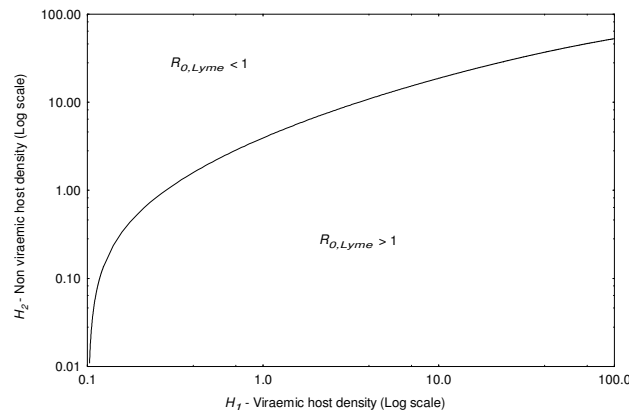

FIG. 5. The effect of hosts densities on $R_{0,Lyme}$. The parameter values are those reported in Tables 1 and 2 with $q^N=q^A=0.3$, γ=0.01 and α=0.005.

Fig. 5 shows that a very little density of rodents (H_1) is needed in order to make the borrelia persist in the system. As previously mentioned, the density of non-viraemic hosts H_2, roe deer in this case, has a negative effect on $R_{0,Lyme}$ ('dilution effect'). Starting from a point (H_1,0) where $R_{0,Lyme}$ >1, in order to make $R_{0,Lyme}$ becomes lower than 1 we need an unrealistic high value of roe deer for sensible value of rodents, note the logarithmic scales

in Fig. 5. Hence we can confirm the finding of Fig. 3A saying that for our parameter values the 'dilution effect' does not occur.

5.4.2 Tick-borne Encephalitis

Also here, we let one parameter vary at a time (Fig. 6), while all other parameters are set at the values listed in Tables 2 and 3 while for the uncertain ones we start using: $\lambda_{LN}=_{NN} =0.65$.

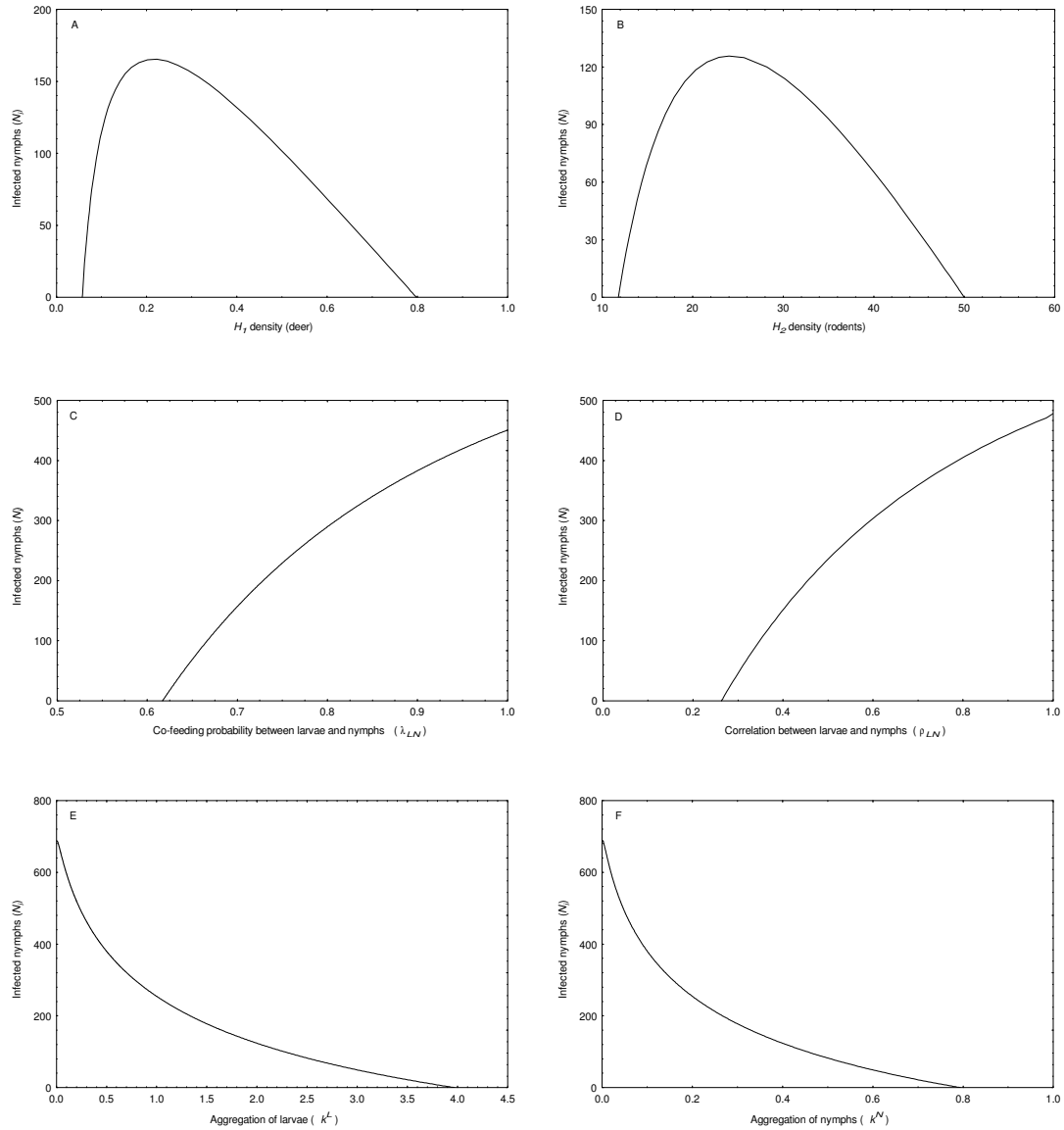**FIG. 6**. Variation of the equilibrium level of infected nymphs N_i with H_1 (Fig. A), H_2 (Fig. B), λ_{LN} (Fig. C), ρ_{LN} (Fig. D), k^L (Fig. E) and k^N (Fig. F).

For this set of parameters we find a positive equilibrium point at: $L \approx 700$, $N_s \approx 578$, $N_i \approx 114$, $A_s \approx 51$, $A_i \approx 38$ and the reproduction number for the disease we get $R_{0,\text{TBE}} \approx 1.09$. We remark that the chosen values for λ_{LN} and λ_{NN} seem to be too high being products of three different probabilities but we need these values to obtain persistence of TBE ($R_{0,\text{TBE}} > 1$).

In this case we observe a 'dilution effect' due to the increase of roe deer density, in fact (as shown in Fig. 6A) as H_1 is increased, the equilibrium value of infected nymphs after a initial increas start decreasing and drop to 0 when H_1 reach the value approx. of 0.8. It means that for higher values of roe deer we have $R_{0,TBE} < 1$. This dilution effect is due to the wasting tick bites on roe deer as they do not take part to the infection processes (co-feeding occur only on rodents). Interestingly, we observe that for TBE also an increase of rodent density might cause a 'dilution effect' (Fig. 6B). In fact for values of H_2 larger than 50, $R_{0,TBE}$ becomes lower than 1 and the virus dies out. However, the reasons of this decrease of $R_{0,TBE}$ are completely different from those due to deer increase. In fact, this is because with an high density of rodents, many ticks will feed on them, but each individual rodent will be carrying very few ticks, so that the probability of finding co-feeding ticks will be relatively low; hence, non-viraemic transmission will become insignificant and, by assumption, viraemic transmission is impossible.

As expected, the density of infected nymphs increases with increasing λ_{LN}, that is the co-feeding probability between infected nymphs and larvae. The threshold value is at $\lambda_{LN}=0.62$ (Fig. 6C).

Figs 6D, 6E and 6F show the quantitative effect of the pattern of tick distributions on the number of infected nymphs at the equilibrium. As expected a stronger aggregation of larvae (Fig.6E) and nymph (Fig. 6F) distribution increases the number of infected nymphs. The same effect is obtain for a strong correlation between larvae and nymphs (Fig. 6D).
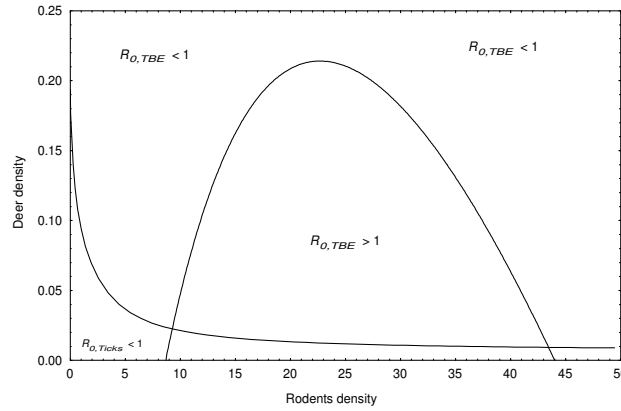
FIG. 7. The effect of host densities on $R_{0,TBE}$ and $R_{0,ticks}$. The parameter values are those reported in Tables 2 and 3 with $\lambda_{LN}=\lambda_{NN}=0.65$.

In Fig. 7 the persistence-extinction boundary that determines the densities of rodents and roe deer that must be present for ticks and TBE virus to persist is shown. For ticks we obtain the same boundary as for Lyme while the shape of the curve $R_{0,TBE}=1$ are rather different and reflect the double 'dilution effect' (of both roe deer and rodents) showed in Fig. 6A and 6B and previously discussed.

5.5 Discussion

In this paper, we applied a general model for tick-borne diseases (Rosà *et al*., 2003) to two emerging diseases in Trentino: Lyme Diseases and Tick borne Encephalitis. The biological assumptions which lead to these special cases are rather different; for Lyme Disease we assume that the only route of transmission is the viraemic (or bacteriemic) transmission between ticks and small mammals (rodents), while for tick-borne encephalitis the unique route of transmission present in the system is the non-viraemic transmission through co-feeding ticks which might occur on small mammals. Other hosts, like deer for instance, are classified as tick maintenance host and they simply amplify the tick population without amplifying the pathogens.

With our parameter estimates the basic reproduction number for Lyme Diseases in Trentino results fairly higher than 1, even though for some parameters included in the formula of $R_{0,Lyme}$ we do not have sensible estimates and so we used only educated guesses. Using intermediate values for the most uncertain parameters we obtain R_0 for Lyme larger than 10 and at the endemic equilibrium 20% of rodents and 15% of nymphs result infected with *Borrelia burgdorferi* s.l. These results fit quite well with the observed value obtained in Trentino where the prevalence of infection in *Apodemus* and *Clethrionomys glareolus* range from 15 to 20% (Rizzoli *et al.*, unpublished data); in *Ixodes ricinus* nymphs the observed prevalence of infection is 17.5% (Rizzoli *et al.*, 2002).

On the contrary, the basic reproduction number for TBE is low. In order to obtain $R_{0,TBE}$ larger than 1 and make the virus persist we need an unlikely high value of λ_{LN} (co-feeding probability between infected nymphs and larvae). This problem may come from errors in parameter estimates (for instance the chosen values for the moulting success for ticks could be too low), or from the lack of relevant factors in the model considered here.

One of the most interesting result obtained from our simulation was the effect of host densities on the persistence of the diseases (Figs. 5 and 7). The effect is rather different for the two diseases considered in this paper. For Lyme we found that the dilution effect due to the high density of non-viraemic host (roe deer) practically does not occur. In fact it happens but for unrealistic high values of roe deer for sensible densities of rodents in Trentino (range from 5 to 30 per hectare). On the other hand, for TBE we observed a convex shape of the persistence-extinction boundary. It means that when there are either too many deer or too many rodents, R_0 becomes less than 1 and the virus cannot persist in the system. This 'double' dilution effect is the results of two different biological mechanism. The first is due to the wasting tick bites of ticks on roe deer while the second happens because with an high density of rodents, many ticks will feed on them, but each

individual rodent will be carrying very few ticks, so that the probability of finding co-feeding ticks will be relatively low; hence, non-viraemic transmission will become insignificant and, by assumption, it is the only route of transmission for TBE. This latter result is supported by some field observation in Trentino (Perkins *et al.*, unpublished data) where it has been observed that the higher values of TBE prevalence was found in sites where the rodents density was at an intermediate level, while sites with lower or higher rodent density show lower values of TBE prevalence.

Finally, if we apply the joint threshold host density curves obtained with our models to the average observed value of rodents and roe deer density in Trentino we observed that for Lyme we are clearly in the region with $R_0 > 1$ and far from the extinction boundary. On the contrary, for TBE the observed host densities are very close to the boundary. This result may indicate that for TBE in Trentino variation in rodent and deer densities can make the virus persist or not and this could explain its hot-spotted distribution in Trentino and in many parts of Europe. On the other hand, Lyme diseses persistence seems to be less influenced by host densities in Trentino where Lyme is endemic in many areas with a very widespread distribution.

To conclude we remark that much more research on the parameter estimation and on the properties of the system is needed to improve our model prediction. Certainly, one of the factors missing in these models is seasonality, which has instead a profound effect on tick dynamics and on transmission of both diseases considered in this paper.

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6. General discussion and future research directions

The main aim of this Thesis was to improve the general understanding of the role played by parasite aggregation in the dynamics of host-parasite interactions, looking specifically at macroparasitic infections and tick-borne infections in wildlife.

Throughout the Thesis, we followed a mathematical approach that consisted of developing mathematical models, then analysing their equations and determining, when it was possible, analytical results such as thresholds, equilibria, periodic solutions and their stability. These mathematical techniques combined with computer simulations permit us to identify and quantify the importance of several parameters, and in particular the role of parasite aggregation on the dynamics of host-parasite interaction.

One of the most important results obtained with the macroparasite models (Chapter 2) is that the mechanism producing aggregation in parasite distributions has a strong influence on the stability of the system. As well known, there exists a tension in host-macroparasite models between stabilizing and destabilizing factors: when the former prevail, at least one equilibrium is stable, and the system will settle to one of those; on the other hand, when destabilizing factors prevail, sustained oscillations will occur. Anderson and May (1978) found that parasite aggregation is a very stabilizing factor. In a sense, we confirm this finding; however, we found that the aggregation produced through our model of host heterogeneity stabilizes the system much more than that obtained through multiple infections (Rosà *et al.*, 2002). Furthermore, in the Anderson and May model parasite aggregation does not influence the threshold for parasite establishment while in our model with multiple infections a large aggregation makes it more difficult for parasites to both regulate hosts, and to get established into a population at carrying capacity. This fact has

an intuitive explanation: a large aggregation causes many hosts to escape from infection; hence, these hosts may be enough to let the population continue growing. Moreover, when we consider parasite establishment, a large aggregation would cause most parasites to occur in the same hosts; hence, even when parasites are extremely rare, they would suffer from increased host mortality due to other parasites. We would therefore expect that the threshold for establishment should increase with the level of aggregation.

These important findings suggest that before applying a model and making predictions about host-macroparasite interactions it is very important to understand the biological mechanisms responsible for generating aggregation in parasite distribution.

While the qualitative dynamics of host-macroparasite systems are mainly based on deterministic models, individual-based simulation models related to host-parasite interactions are becoming increasingly popular (Wilber and Shapiro,1997; Peters and Lively, 1999). In simulation models, one can easily introduce many important factors missing from simple deterministic models, such as spatial structure with local interactions (Hess, 1996; Keeling, 1999), genetical and behavioural differences among individual hosts. However, if the rules of simulation models are very complex, it becomes difficult to disentangle the effect of the different factors, and to obtain a clear qualitative understanding of the deterministic models.

In Chapter 3 we restricted our considerations to simulation models (Rosà *et al.*, 2003) that may be considered the stochastic counterpart of the deterministic models considered in Chapter 2. The stochastic simulations show that the results of deterministic models mainly hold when demographic stochasticity is added. We found that the average values of host density, parasite burden and parasite aggregation are close to the value at the deterministic equilibrium, and show similar trends with respect to their relationship to the parameters. With the stochastic model we also found that the persistence of host-parasite

interaction is not guaranteed by the condition $R_0>1$ and strongly depends on the host carrying capacity. Introducing density-dependence in parasite demographic traits, increases persistence somewhat. However when we allowed for infections from an external parasite reservoir, we found that host extinction may easily occur.

We note that the simulations presented in Chapter 3 are very simple, since we assumed homogeneous mixing of host and parasite, neglecting spatial and social structure of hosts, temporal changes in environmental factors that may influence tarsnmission, as well as parasite induced acquired immunity. These simulations can however be the basis on which more complex simulations can be built, as well as the reference against which their results may be assessed.

In tick-borne infection model (Rosà *et al.*, in press, Chapter 4), we consider specifically the possibility of non-viraemic transmission that is thought to be crucial in the maintenance of several infections such as Tick-borne Encephalitis (Randolph *et al.,* 1996; 1999; 2002). We also considered the distribution of tick stages among hosts, which proved very important in facilitating the transmission through co-feeding (Randolph *et al.*, 2002; Perkins *et al*., in press).

We obtained an explicit formula for the threshold for disease persistence in the case of only viraemic transmission and in the case of both viraemic and non-viraemic transmission. From this formula, the effect of parameters on the persistence of infection has been investigated. When only viraemic transmission occurred, we confirm that, while the density of the competent host always had a positive effect on infection persistence, the density of the incompetent host may have either a positive effect, by amplifying tick population, or a negative ("dilution") effect, by wasting tick bites on an incompetent host. With non-viraemic transmission, the "dilution" effect becomes less relevant. Including the effects of tick aggregation on hosts and correlation of tick stages we found that a large

aggregation in ticks and a strong correlation between different tick stages cause a big increase in the basic reproduction number of the infection.

As well known, heterogeneity in host populations can generate aggregation in parasite distributions among hosts (Anderson and Gordon, 1982). We found that both in macroparasites and tick-borne diseases, the level of aggregation influenced the basic reproduction number of the infection, and consequently the persistence of the disease in the system. Aggregation in those macroparasites species that increase the mortality of their hosts makes it more difficult for the establishment of parasite in the host population and so the basic reproduction number of parasite decreases for higher values of parasite aggregation. On the other hand, aggregation of tick distribution in hosts, on which non-viraemic transmission occurs, increases the basic reproduction number of the pathogen transmitted by ticks. This difference is due to the fact that in this case aggregation does not concern the parasite responsible for the disease but the vector. In a sense, a large aggregation of tick distribution on hosts where co-feeding transmission takes place has the same effect of a high concentration of hosts in space for a directly transmitted microparasitic disease.

On the whole, this work has emphasized the importance of considering heterogeneities in the modelling of host-parasite interactions. For instance, not including aggregation of tick distribution in hosts on which non-viraemic transmission takes place might cause an underestimate of the basic reproduction number of the infection and this may give us the wrong signals when considering the possible strategies for disease control. Even more important is modelling the biological mechanisms that produce aggregation in parasite distributions rather than describing aggregation with some population parameters, such as k of the Negative Binomial distribution that does not correspond to any biological process, but is instead a population statistics. We followed this approach for

macroparasites models finding that different mechanisms that produce aggregation cause different host-parasite dynamics. However this did not apply for tick aggregation and this represents an important aspect to consider in the future.

One of the factors missing in the models considered in this Thesis, both for macroparasites and tick-borne infections, which can have a profound effect on infection transmission is seasonality (see for instance White *et al.*, 1996, for macroparasites and Randolph *et al.*, 1999, for ticks). Thus, another important future avenue of research will be to introduce seasonality in these models, although probably explicit expressions will no longer be computable.

One of the advantages of using epidemiological models is to get explicit formulae for determining thresholds, equilibria, periodic solutions and providing a clear understanding of disease dynamics. This makes models very important tools for identifying possible strategies for disease control. However, before using models as a management tool for planning control and prevention programs, detailed empirical studies have to be carried out to assess model results. In fact, it has been demonstrated that sometimes model predictions are in disagreement with empirical evidences. This is the case for cowpox infection in rodents (Begon *et al.,* 2003) where it has been found from field observation that there is a little support for density-dependent transmission, despite this having been the usual default assumption in models for non-sexually transmitted infections. This highlights the fact that little attention has been paid in the past to the practical meaning of some theoretical concepts obtained with models. Wildlife-disease modelling remains an essential tool for understanding the increasing flood of data on population and heterogeneities in hosts and pathogens. There has been much progress in this area; however, further advances are urgently required in terms of model validation hoping that the 'distance' between empiricist and theoreticians will decrease in the near future.

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