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Lyme Disease: Self-regulation and Pathogen Invasion

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Ecological interactions underlying the epidemic of Lyme disease involve a spirochete, a tick (with larval, nymph and adult stages), and two (or more) vertebrate hosts. Juvenile ticks ordinarily feed on mice; adult ticks feed on deer. Mice acquire the spirochete from infected nymphs and then pass the infection to larvae of the next tick generation. Lyme disease may result when a human is inadvertently bitten by an infectious nymph.

Our model of the Lyme phenomenon counts the total number of ticks in each stage, the numbers of infected ticks by stage, and the number of infected mice. We fix the total population sizes of deer and mice, assume the ticks self-regulate, and solve the homogeneous-mixing case for equilibrium abundances. A local stability analysis identifies a condition where extinction of the spirochete is stable. Reversing this condition implies that the spirochete can invade the system of ticks and vertebrate hosts. When the spirochete can invade, a positive equilibrium number of infected organisms is locally stable. Spirochete invasion is promoted by a sufficient density of mice suffering low mortality, high susceptibility to infection in both mice and ticks, a high attack rate of ticks on mice, a high density of larval ticks, and low mortality among tick nymphs. Low mouse mortality allows the frequency of infection among nymphs to approach an individual tick's susceptibility when feeding on an infected mouse.

1. Introduction

Lyme disease remains the most frequently reported vector-borne disease of humans in the United States (Tsai *et al.*, 1989; Miller *et al.*, 1990; Barbour & Fish, 1993) and the world's most common tick-borne infection (Bennett, 1995). New cases appear at unabated rates in endemic areas, and the geographic distribution of the incidence of Lyme disease has expanded rapidly (Wilson *et al.*, 1990; White *et al.*, 1991; Ginsberg 1993). The processes underlying the spread of the disease involve direct interactions among no fewer than four species (Spielman *et al.*, 1985; Sandberg *et al.*, 1992; Ostfeld *et al.*, 1995). Consequently, ecological concepts should offer a predictive understanding of the phenomenon (Van Buskirk & Ostfeld, 1995).

Lyme disease is a zoonosis; humans acquire a pathogen that ordinarily infects other species. In the northeastern United States the infectious agent is a spirochete *Borrelia burgdorferi*. The hematophagous vector is the deer tick *Ixodes scapularis* (following Ostfeld *et al.*, 1995), formerly designated *I. dammini*. Larval and nymphal ticks feed primarily on the white-footed mouse *Peromyscus leucopus*, but will attack a variety of hosts; inadvertent nymph bites can infect humans with the spirochete. Adult ticks feed preferentially on white-tailed deer *Odocoileus virginianus*. Our models focus on these four species, and we let infection in humans follow as a consequence of the community's population dynamics. Different strains of *Borrelia*, and different species of tick vectors and vertebrate hosts, are found in different geographical regions (Lane & Loye, 1991; Bennett, 1995). Despite

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the emphasis of our model, the qualitative results may elucidate general characteristics of various spirochete–tick associations found across the northern hemisphere (see Lane *et al*., 1991; Barbour & Fish, 1993; Ginsberg, 1993). A series of observations motivates our analyses:

1. Modeling Lyme disease within the context of vector and host population dynamics may identify priorities for empirical research, and may offer a mechanism for evaluating control policies (Sandberg *et al*., 1992; Van Buskirk & Ostfeld, 1995).
2. Some recent advances in ecological theory have been attained with multi-species models that combine different types of pairwise interactions (e.g. Holt & Pickering, 1985; Anderson & May, 1986; Hochberg *et al*., 1990; Begon & Bowers, 1995). Similarly, models where different stages of a single species experience different ecological interactions have produced novel insights (e.g. Gordon *et al*. 1991, Briggs & Godfray, 1995).
3. Pathogens may sometimes regulate population densities of their hosts (e.g. Anderson & May, 1981; Dobson & Hudson, 1986, 1995; Begon *et al*., 1992). In the case of the Lyme phenomenon, *Borrelia* can induce disease symptoms in individual mice (Burgess *et al*., 1990), but field studies have not yet suggested that mouse population dynamics are strongly affected by the spirochete (see Gage *et al*., 1995). Increasing the abundance of mice can only promote the development of juvenile ticks (Hazler & Ostfeld, 1995), but the ecological effect of ticks on mice is unclear. Tick bites can evoke an immune response in their hosts (e.g. Bennett, 1995). But a mouse capable of grooming apparently does not become so infested that its survival is clearly impaired (J.S. Mackiewicz, pers. comm.). Consequently, tick parasitism may ordinarily have little effect on mouse population dynamics. Given the present uncertainty concerning interspecific population regulation in this system, the model in this manuscript assumes that vertebrate hosts are essentially self-regulating. The results will provide a comparison for models where parasitism or the pathogen's virulence may affect the dynamics of mouse populations.

These three points guide our initial modeling, at each of two distinct spatio-temporal scales. Our first models for the Lyme phenomenon were spatially explicit, individual based models (Deelman *et al*., 1995, 1997); they addressed effects of behavior on population patterns at a local scale (within-habitat and within-year). The present model characterizes the Lyme phenomenon at the population level and will serve as a point of departure for a regional model, where local demes are linked through dispersal.

We organize this manuscript as follows. First, we outline the natural history associated with Lyme disease. The outline appreciates the biological complexity of the problem, while suggesting a tractable analysis. Second, we present our model; we assume homogeneous mixing and investigate equilibria and stability analytically. The assumption of self-regulation allows us to decouple the dynamics of total population sizes from rates of change in the number of infected mice and infected ticks. This simplification lets us examine the spirochete's invasion of a two host-parasite community at equilibrium.

2. Lyme Disease: Biological Background

We merely sketch the natural history of the Lyme phenomenon; for additional detail see Wilson *et al*. (1990), Barbour & Fish (1993), Ginsberg (1993), or Ostfeld *et al*. (1995). *I. scapularis* exhibits a two-year life cycle. As many as 90% of newly hatched larvae attack white-footed mice (Spielman *et al*., 1985). Some of the remaining larvae attach to other vertebrates, including birds, and may be dispersed over relatively long distances (e.g. Ginsberg, 1993). Larvae that obtain a blood meal drop off their host and then overwinter as nymphs. At the beginning of the second year, nymphs "quest" for a blood meal (the second of the life cycle). If they succeed, the nymphs may mature to the adult stage. Adults (adult females) feed almost exclusively on white-tailed deer, and all mating occurs there. Females eventually drop off the deer they have parasitized, lay their eggs nearby, and die. A female that has engorged and subsequently mated produces around 2000 fertile eggs, and nearly all hatch (Sandberg *et al*., 1992).

Transplacental transmission of the spirochete does not occur in mice, or is extremely rare (Burgess *et al*., 1993). That is, an infected mouse does not vertically infect its offspring; a mouse is infected only via a tick bite. Spielman *et al*. (1985) assume that transovarial transmission of the spirochete in ticks can be neglected because of rarity. Piesman (1988) indicates that no more than 1% of newly hatched larvae acquire the infection transovarially. Hazler & Ostfeld (1995) suggest that the rare infected larvae may be individuals that were groomed from an infected mouse before they finished their blood meal. Since transovarial transmission of the spirochete is at most uncommon, our model ignores the possibility.

Mice and ticks are infected or susceptible, depending upon the presence or absence of *Borrelia*.

In areas where Lyme disease is endemic, Ginsberg (1993) estimates that 20–33% of nymphs (ticks that have previously taken a single blood meal) are infected, and that 50% of questing adults (having already taken two blood meals) are infected with the spirochete. The white-tailed deer's resistance to infection (Wilson *et al*., 1990) is not important epidemiologically, since it is the tick to mouse to tick enzootic cycle of infection that maintains the spirochete. The seasonally ''inverted'' pattern of abundance of the tick developmental stages helps drive the cycle. Nymphs infected last year appear first as warmer weather begins; these ticks pass the spirochete to susceptible mice. After summer has arrived (July and August), larvae hatch, quest for a blood meal and acquire the spirochete when they attack an infected mouse. These individuals then become quiescent as infected nymphs, completing the cycle of infection.

3. Self-regulation and the Lyme Phenomenon

Our model assumes homogeneously mixing populations of deer, mice and ticks. We fix the number of deer at H^*. The total number of mice is also a constant, M^*, but the number of infected mice can vary. For mice, we assume that density-dependent reproduction (e.g. Begon *et al*., 1992) imposes a carrying capacity K_M. r_M is the intrinsic rate of increase for mice, and μ_M is the density-independent mortality rate; control measures might act through μ_M. We assume $r_M > \mu_M$, so that the total number of mice is $M^* = K_M(1 - \mu_M/r_M)$. The following continuous variables characterize the community at time t:

H^*: Total number of deer
M^*: Total number of mice
V_t: Total number of larval ticks
N_t: Total number of tick nymphs
A_t: Total number of adult ticks
m_t: Number of infected mice
n_t: Number of infected nymphs
a_t: Number of infected adult ticks

Numbers of infected organisms change through transmission of the spirochete and death; we assume no recovery. In the absence of transovarial infection, spirochete transmission always requires the tick–mouse interaction. The spirochete cannot survive in soil, water or air (Barbour & Fish, 1993), so that infection from the abiotic environment does not occur.

Sandberg *et al*. (1992) numerically model the development and infection of a tick population with a series of 12 matrices, each representing the changes occurring within a particular month. Some general results for that model are given in Awerbuch & Sandberg (1995). Van Buskirk & Ostfeld (1995) present a set of difference equations and simulate the growth of a tick population. Tick reproductive processes are closer to seasonal than continuous. But the spirochete infection processes are closer to continuous. Our model is written in continuous time; for comments on continuous-time models of parasitic organisms with discrete developmental stages, see Gordon *et al*. (1991) or Ives (1992). A continuous-time formulation essentially ''wraps'' consecutive spring/summer seasons. The analysis is restricted to attainable equilibrium abundances; the total and infected numbers of mice and tick stages at any time will equal the serial abundances a tick–mouse cohort experiences from birth to death. Our model does not address stability differences between discrete and continuous-time models, or differences in dynamics away from equilibrium, but the biological significance of the results should not be restricted by the continuous formulation.

3.1 TOTAL TICKS

Adult ticks attack deer, females (and perhaps males, Bennett, 1995) take a meal, and are then capable of reproducing. We assume self-regulation in tick reproduction, although intraspecific competition may act elsewhere in the tick life cycle (Van Buskirk & Ostfeld, 1995). Some studies imply that ticks may self-regulate (e.g. Sutherst *et al*., 1973; Randolph, 1994); others find no evidence for any density dependence (e.g. Fish, 1993). For a general discussion, see Dwyer (1994).

We quantify tick reproduction as the rate at which eggs hatch, hence the rate at which larvae begin questing for their first blood meal. A_t is the total number of adult ticks. The constant α_H converts attacks by adult ticks on deer into a component of tick reproduction (Table 1 defines all parameters of

TABLE 1
Model parameters

α_H	Rate at which adult ticks attack deer
c	Scales self-regulation in tick reproduction
f	Larvae hatching per adult tick–deer interaction, in absence of tick self-regulation
α_M	Rate at which juvenile ticks attack mice
μ_V	Mortality rate per larva
D'	Rate at which larval ticks attack hosts other than mice
μ_N	Mortality rate per nymph
γP	Rate at which a nymph bites humans
μ_A	Mortality rate per adult tick
β_M	Susceptibility of mice to spirochete infection
β	Susceptibility of ticks to spirochete infection
μ_M	Mortality rate per mouse

the model). c scales the effect that crowding among adult ticks exerts on their reproduction. Let the function $F_V(A_t)$ represent the rate at which larvae hatch from eggs:

$$F_V(A_t) = A_t\,[\alpha_H f H^* - cA_t] \tag{1}$$

where f represents the average number of eggs hatching per adult attack on deer in the absence of intraspecific competition; below we refer to the product $\alpha_H f$ as the ticks' intrinsic rate of increase. The tick population cannot grow unless deer are sufficiently abundant. More specifically, non-negativity of F_V requires a deer population large enough that $H^* \geqslant cA_t/\alpha_H f$. In turn, this implies that $0 \leqslant A_t \leqslant (\alpha_H f H^*/c)$. This range for the total number of adult ticks includes not only extinction, but also the positive equilibrium value we describe below.

A brief consideration of individual fecundity, $F_V(A_t)/A_t$, reveals the more important assumptions about tick reproduction. Fecundity increases linearly with the density of deer, so that each unit of "resource" has the same positive effect on an individual adult tick's reproduction. Fecundity declines linearly as the density of adult ticks increases, the standard representation of logistic self-regulation. Essentially, the quadratic form of eqn (1) serves to approximate more complex effects of adult density on the rate at which larvae are added to the population (Begon *et al*., 1992; Norman *et al*., 1994).

The total numbers of larvae, nymphs and adult ticks, respectively, change according to:

$$\mathrm{d}V_t/\mathrm{d}t = A_t(\alpha_H f H^* - cA_t) - V_t(\alpha_M M^* + \mu_V + D') \tag{2}$$

$$\mathrm{d}N_t/\mathrm{d}t = V_t(\alpha_M M^* + D') - N_t(\mu_N + \alpha_M M^* + \gamma P) \tag{3}$$

$$\mathrm{d}A_t/\mathrm{d}t = \alpha_M M^* N_t - \mu_A A_t \tag{4}$$

α_M is the attack rate of immature (larval or nymphal) ticks on mice. Equation (2) shows that larval tick numbers increase with F_V, and decrease as they attack mice and mature to the nymphal stage, and as they die; μ_V is the larval mortality rate. Deer ticks apparently lack significant predators, but larvae and nymphs suffer elevated mortality during inclement weather (Barbour & Fish, 1993).

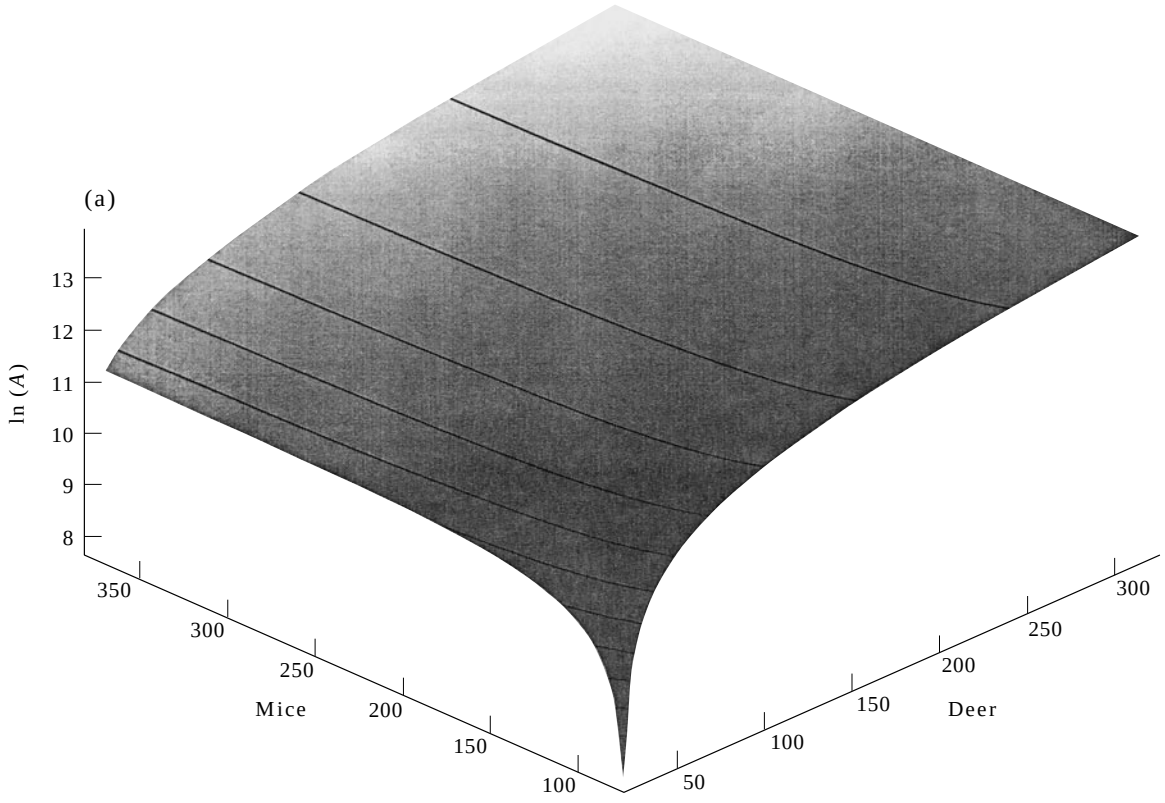

FIG. 1(a)

Some larvae attach to birds, pets or small mammals other than mice (Ginsberg, 1993). D' is the rate at which larval ticks attack hosts other than mice. Since most larvae that advance developmentally feed on mice, we treat D' as a density-independent constant. But attacks on hosts other than mice are important, because they reduce the number of larvae exposed to infectious mice and, consequently, almost certain transmission of the spirochete (Van Buskirk & Ostfeld, 1995; see Discussion).

Equation (3) shows that the total number of nymphs increases as larvae attack mice and feed, and through maturation of larvae that attack other hosts. Nymphs decline through natural mortality, and by advancing to the adult stage after feeding; μ_N is the nymphal mortality rate. Some additional nymphs are lost from the normal life-stage progression because they bite humans. P is the number of humans exposed to nymphal ticks; we leave P constant. Nymphs attack humans at rate γ; this includes bites by both infected and uninfected ticks. In eqn (4) adult ticks arise from nymphs that successfully attack a mouse and feed. μ_A is *per capitum* adult mortality; μ_A averages over adult ticks that feed on deer and those that do not find a host.

3.2 INFECTED MICE AND TICKS

Assuming no larva is infected prior to its first blood meal (Piesman, 1988), mice acquire the spirochete from infected nymphs only. Then the number of mice infected with the spirochete changes according to:

$$\mathrm{d}m_t/\mathrm{d}t = \alpha_M\beta_M(M^* - m_t)n_t - \mu_M m_t \qquad (5)$$

n_t is the number of infected tick nymphs, and β_M represents the susceptibility of a mouse to infection by the spirochete when the mouse is bitten by an infected tick. $(M^* - m_t)$ is the number of susceptible mice. The numbers of infected tick nymphs and infected adults, respectively, change according to:

$$\mathrm{d}n_t/\mathrm{d}t = \alpha_M\beta V_t m_t - n_t(\alpha_M M^* + \mu_N + \gamma P) \qquad (6)$$

$$\mathrm{d}a_t/\mathrm{d}t = \alpha_M[M^* n_t + \beta(N_t - n_t)m_t] - \mu_A a_t \qquad (7)$$

β is susceptibility of a tick, larva or nymph, to spirochete infection when the tick feeds on an infected mouse. $(N_t - n_t)$ is the number of susceptible nymphs.

Once infected, mice apparently do not lose the spirochete (Barbour & Fish, 1993; but see De Boer *et al*., 1993). Therefore, eqn (5) does not include any recovery of infected mice. In eqn (6) infected tick nymphs arise after susceptible larvae have fed on

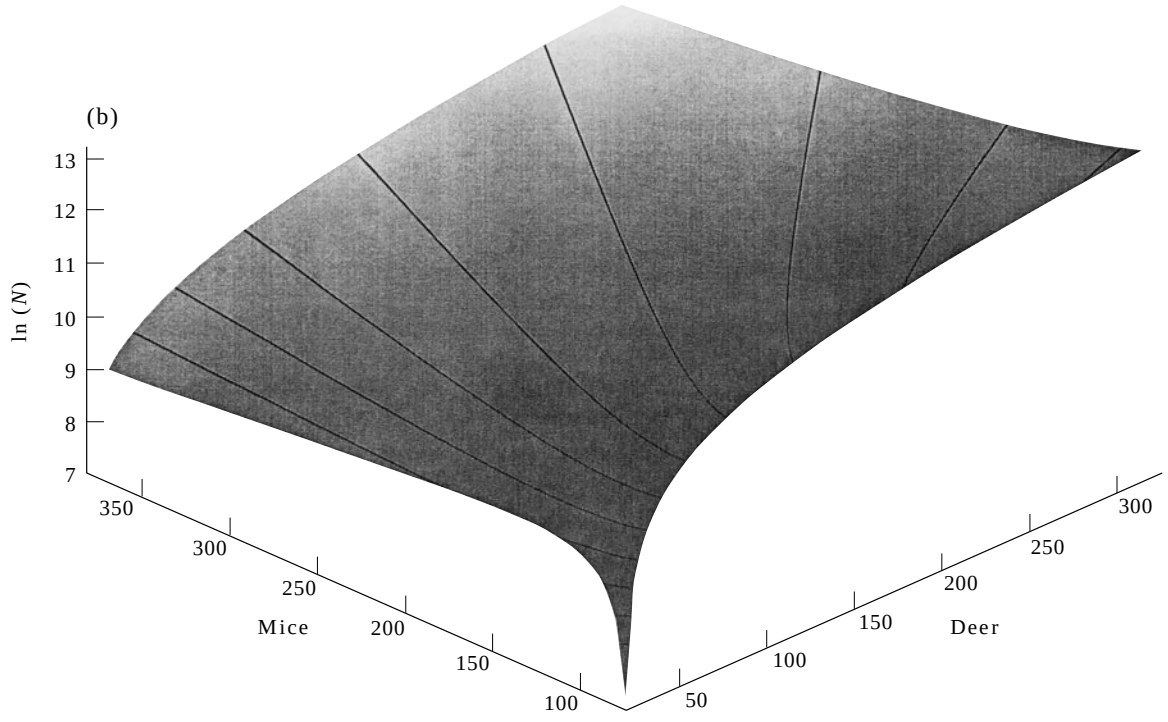

FIG. 1(b)

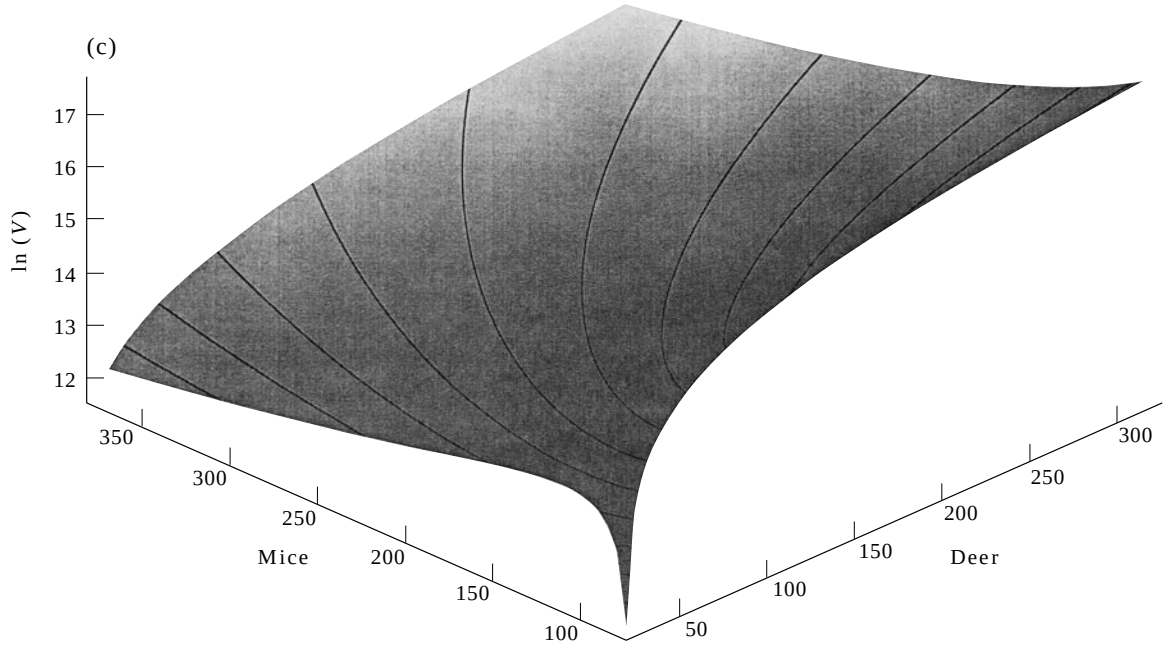

FIG. 1(c)

FIG. 1. Global tick abundance at equilibrium. (a) Shows adults, (b) shows nymphs, and (c) shows larvae. Each is plotted logarithmically as a function of deer and mouse population sizes. Parameter values are $\alpha_H = 0.055$, $f = 600$, $c = 0.01$, $\mu_A = 2$, $D' = 1$, $\gamma P = 450$, $\alpha_M = 0.05$, $\mu_V = 12$, and $\mu_N = 6$.

infected mice. The term ($\gamma n_i P$) represents human exposure to Lyme disease; the density of infected tick nymphs is perhaps the most important variable for predicting the incidence of Lyme disease (Mather, 1993). In eqn (7) infected nymphs can feed on any mouse (infected or not) and become an infected adult tick. But an uninfected nymph can become an infected adult only if it feeds on an infected mouse.

4. Equilibria

The model's equilibria yield hypotheses concerning stability and invasability, and offer a comparison for more general models. Assuming that total numbers of deer and mice remain at [H^* M^*] allows us to focus on the pathogen's invasion of its hosts; we recognize the potential effect of vertebrate host dynamics on the spirochete's advance.

4.1 EQUILIBRIUM TICK ABUNDANCES

The dynamics of the total numbers of larval, nymphal and adult ticks depend only on their own densities and the densities of their vertebrate hosts. [V N A] = 0, extinction of the entire tick population, is a feasible equilibrium. The positive equilibrium [V^* N^* A^*] has solution:

$$A^* = \frac{\alpha_H f H^*}{c} - \left(\frac{1}{c}\right)\frac{\alpha_M M^* + \mu_N + \gamma P}{\alpha_M M^* + D'} \times \left[\frac{\mu_A(\alpha_M M^* + \mu_V + D')}{\alpha_M M^*}\right] \quad (8)$$

$$V^* = \frac{\mu_A}{\alpha_M M^*}\left[\frac{\alpha_M M^* + \mu_N + \gamma P}{\alpha_M M^* + D'}\right] A^* \quad (9)$$

$$N^* = (\mu_A/\alpha_M M^*)\, \mathrm{A}^* \quad (10)$$

Feasibility of the positive equilibrium requires a sufficient number of deer so that $A^* > 0$. Then [V^* N^* A^*] > 0 is biologically relevant when, according to expression (8):

$$H^* > \frac{(\alpha_M M^* + \mu_V + D')\,(\alpha_M M^* + \mu_N + \gamma P)\mu_A}{\alpha_H f \alpha_M M^*\,(\alpha_M M^* + D')} \quad (11)$$

Note that A^* is a linear increasing function of deer abundance H^*. Note also that both V^* and N^* are multiples of A^*. Then the combined tick population size at equilibrium, ($V^* + N^* + A^*$), is:

$$\left[\frac{(\alpha_M M^* + D')\,(\alpha_M M^* + \mu_A) + \mu_A(\alpha_M M^* + \mu_N + \gamma P)}{\alpha_M M^*\,(\alpha_M M^* + D')}\right] A^* \quad (12)$$

which is also a simple multiple of A^*.

Figure 1 (a–c) shows A^*, N^* and V^*, each plotted logarithmically as a bivariate function of equilibrium deer and mouse population sizes. Several qualitative effects suggested in the figure are retained across most parameter combinations consistent with expression (11). When both deer and mouse populations are relatively small, the abundance of each tick stage increases as the number of either deer or mice is increased. A^* increases with deer abundance, as described above, at any level of M^*. However, at larger deer abundance, the number of adults responds only weakly to the density of mice. N^* and V^*, both proportional to A^*, increase with the number of deer across mouse densities. At low deer abundance both N^* and V^* first increase and then decrease with M^*; hence juvenile tick abundance can be maximal at intermediate mouse densities. But when deer are sufficiently abundant, N^* and V^* vary strictly inversely with the size of the mouse population, although the dependence is relatively weak.

For given mouse abundance, the number of ticks in each stage increases as the density of deer increases, but the relative abundances of the three developmental stages are preserved. For any given deer abundance, increasing a sufficiently large mouse population can decrease N^* and V^*, while still increasing A^*. The relative abundance of both juvenile stages declines because increased numbers of mice promote the rate at which juvenile ticks advance developmentally, but an increased mouse density does not influence the rate at which adult ticks are depleted.

The abundances of the three tick stages further depend, of course, on the choice of parameter values. For example, if both vertebrate host populations are small, tick numbers are sensitive to variation in the attack rates α_H and α_M. But general properties of equilibrium tick numbers, for larger numbers of deer and mice, are summarized by the plots in Fig. 1.

4.2. INFECTION EQUILIBRIA

Equilibrium population sizes do not depend on the numbers of infected organisms, but the reverse is not true. Spirochete extinction, $[m\ n\ a] = 0$, is a feasible equilibrium. Given M^*, V^*, N^*, and A^*, the positive

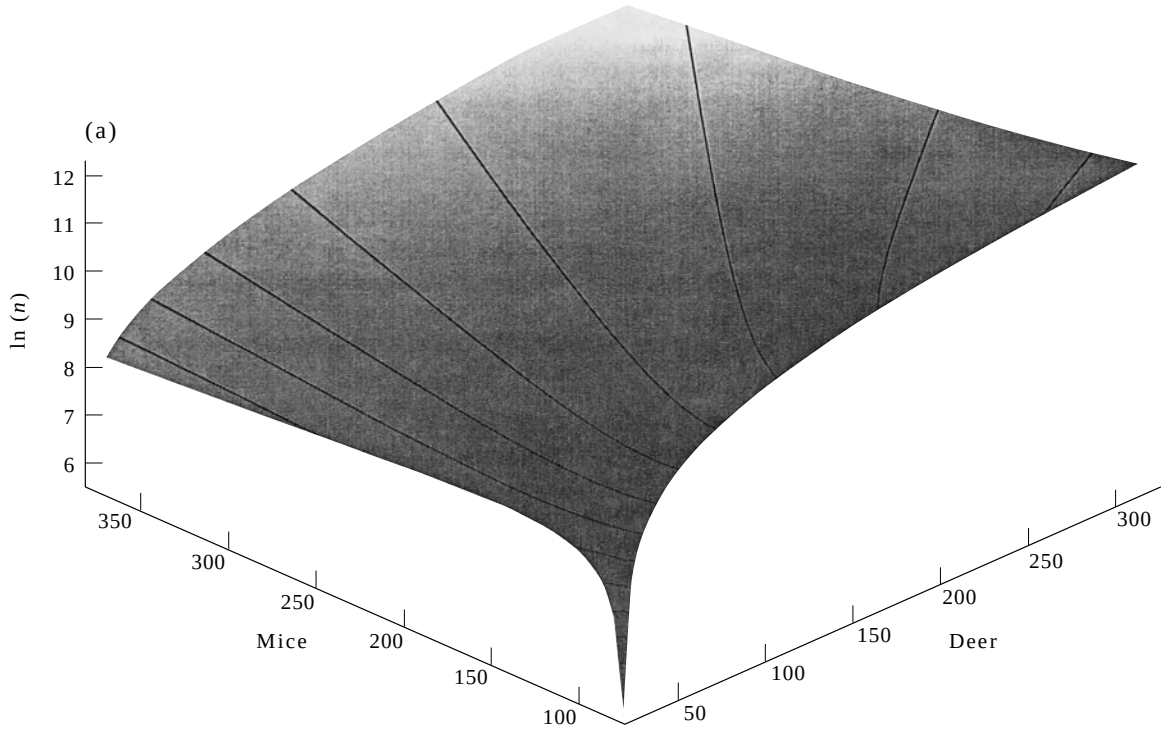

FIG. 2(a).

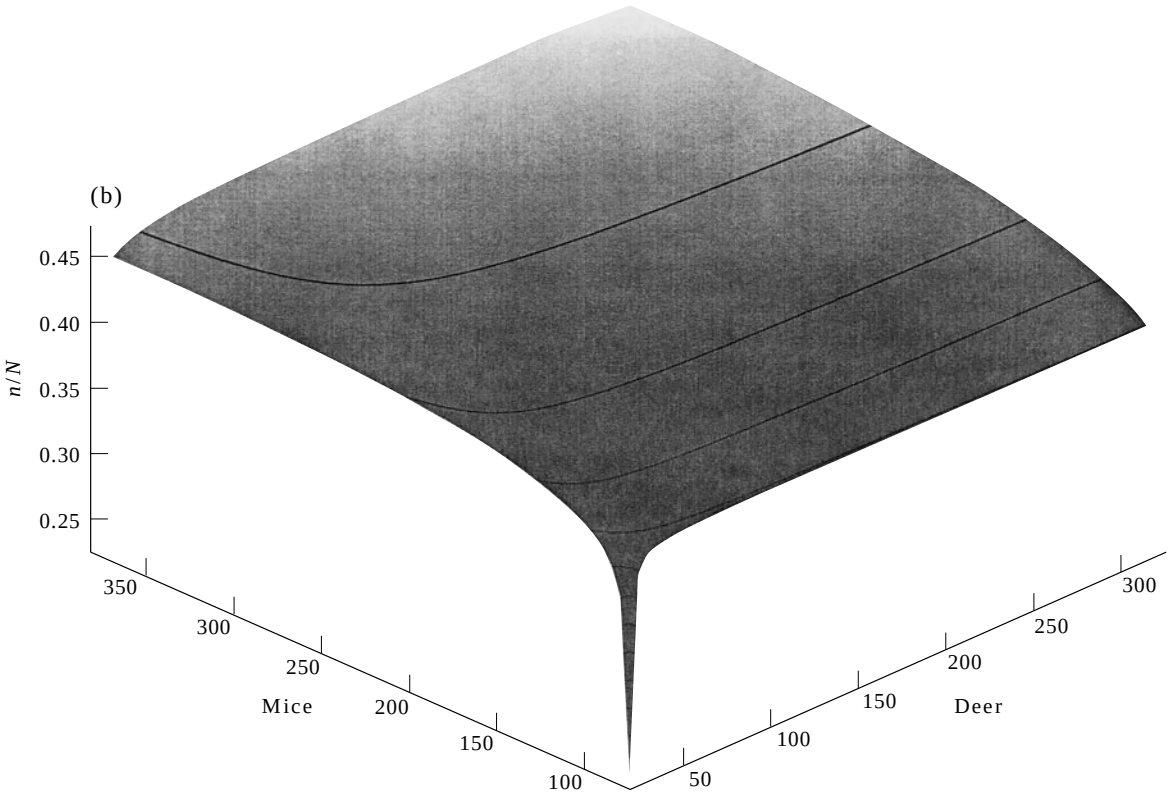

FIG. 2(b)

equilibrium [m^* n^* a^*], from eqns (5), (6) and (7), has solution:

$$m^* = M^* - \frac{\mu_M(\alpha_M M^* + \mu_N + \gamma P)}{\alpha_M^2 \beta_M \beta V^*} \tag{13}$$

$$n^* = M^* \left[\frac{\alpha_M \beta V^*}{\alpha_M M^* + \mu_N + \gamma P} \right] - \frac{\mu_M}{\alpha_M \beta_M} \tag{14}$$

$$a^* = \alpha_M [n^* M^* + \beta(N^* - n^*) m^*] / \mu_A \tag{15}$$

The infectious-nymph equilibrium n^* depends on M^*, and increases with global larval number V^*. Figure 2(a) shows the equilibrium level of infectious nymphs, hence the risk of Lyme disease, scaled logarithmically as a bivariate function of deer and mouse abundances. The number of infectious nymphs follows a pattern similar to that for total nymphs N^*. When both vertebrate hosts are rare, n^* increases as either H^* or M^* is increased. But when the mouse population is larger, n^* declines with M^*. Once deer are sufficiently abundant, n^* always declines with an increase in the number of mice, but the effect is relatively weak.

Figure 2(b) shows the equilibrium frequency of spirochete infection among nymphs (n^*/N^*) as a function of both deer and mouse population sizes. Although the count of infectious nymphs decreases as mouse density increases (for sufficiently large M^*), the frequency of infected nymphs always increases as mice become more abundant. However, the frequency of infected nymphs is independent of the abundance of deer, except when both vertebrate hosts are rare.

In the absence of transovarial infection, the equilibrium frequency of infection among nymphs (n^*/N^*) cannot exceed β, a larva's susceptibility to infection when feeding on an infected mouse. If μ_M is small compared with $\alpha_M \beta_M$, then n^* is a multiple of V^*, and:

$$(n^*/N^*) \approx \beta \alpha_M M^* / (\alpha_M M^* + D') \tag{16}$$

The frequency of infected nymphs approaches β as $\alpha_M M^*$ increases. Applying the same argument to eqn (13), if μ_M is small compared with $\alpha_M \beta_M$, then m^* approaches M^*. The unconditional frequency of spirochete infection among nymphs can approach the conditional probability of infection, given that a mouse is infected, only if most mice carry the

spirochete. Numerical calculations by Van Buskirk & Ostfeld (1995) yield a similar result despite different assumptions about the dynamics of infection transmission.

Figure 2(c) plots the equilibrium frequency of spirochete infection among mice (m^*/M^*) for the same parameter values. When both vertebrate abundances are small, infection frequency increases rapidly as either H^* or M^* increases. (m^*/M^*) quickly becomes independent of deer abundance as H^* increases. When the deer population is large, the frequency of infection among mice also becomes independent of mouse population size.

4.3. INVASION BY THE SPIROCHETE

The primary purpose of this study is to identify conditions that may promote the spirochete's invasion of a host community. We assume that populations of deer, mice, and ticks are at positive equilibrium. In parallel with a standard epidemiological approach (but see Mollison & Levin, 1995), suppose one infected nymph enters the system at equilibrium. We want the condition whereby the spirochete infection advances when rare.

The expected number of mice infected by this single nymph is R_2. We ignore the probability that the nymph bites a human in the condition for invasability; see the discussion of stability below. The nymph attacks, at most, a single mouse, and an attack does not guarantee transfer of infection, so $R_2 < 1$. If the infection is passed to a mouse, let R_1 be the average number of nymphs infected by the initial infectious mouse during its lifetime. R_1 may exceed unity. Let R_0 represent the expected number of nymphs infected as a result of the initial introduction; then $R_0 = R_2\ R_1$. The invasability criterion for the infection is $R_0 > 1$.

The expected number of mice infected by the initial infective nymph is:

$$R_2 = \alpha_M \beta_M M^*/(\alpha_M M^* + \mu_N) < 1 \qquad (17)$$

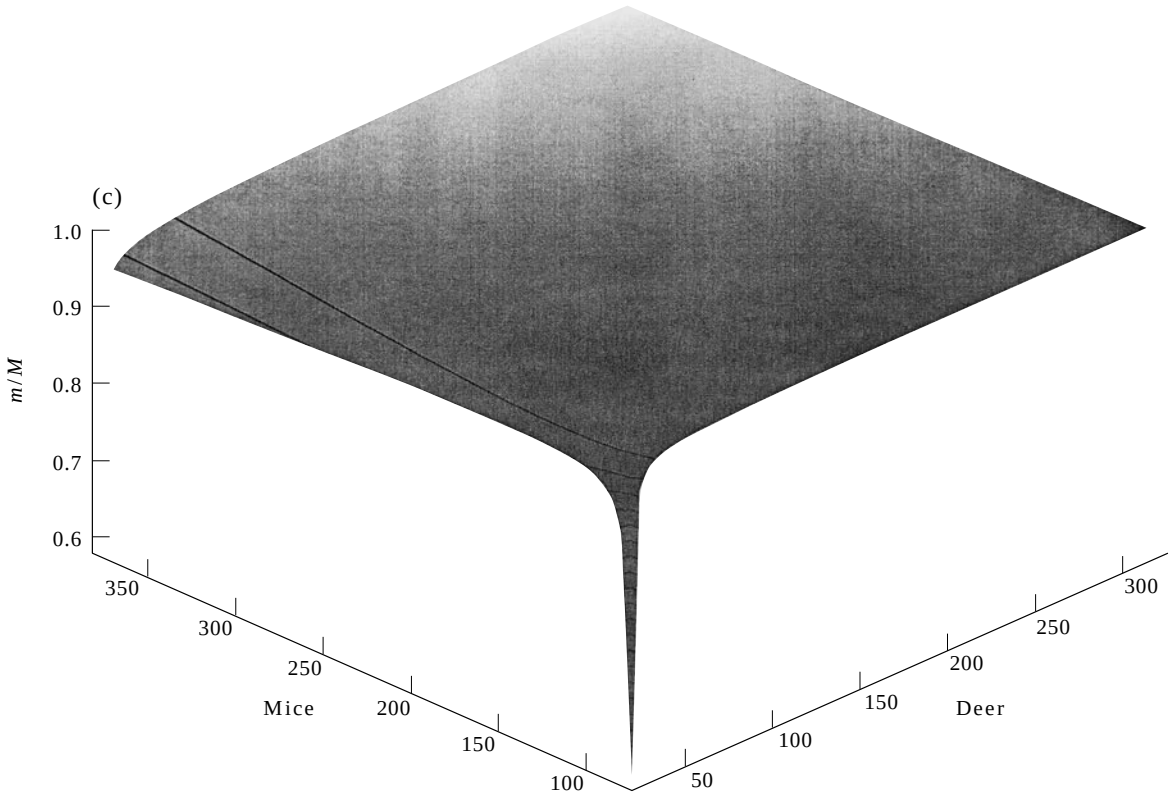

FIG. 2(c)

FIG. 2. Infection frequencies at equilibrium. (a) Shows global abundance of infectious nymphs (scaled logarithmically), (b) shows infection frequency among nymphs, and (c) shows infection frequency among mice. Each is plotted as a function of deer and mouse population sizes. A greater proportion of tick nymphs, and a slightly smaller proportion of mice, are infected as mice become more numerous. Parameter values are the same as Fig. 1, plus $\beta_M = 0.1$, $\beta = 0.5$, and $\mu_M = 1$.

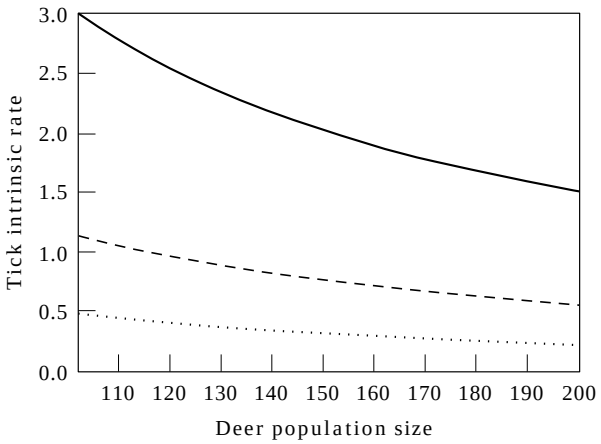

FIG. 3. Stability of total tick population. Abscissa is H^*; ordinate is critical value of $\alpha_H f$ for local stability of positive equilibrium [V^* N^* A^*]. Equilibrium is locally stable below line. Mouse population sizes are 200 (——), 400 (– – –) *and* 800 (.....).

Given transmission of the spirochete, the average number of nymphs infected by the initial infective mouse is:

$$R_1 = \beta\alpha_M V^*/\mu_M \tag{18}$$

Then the spirochete infection advances if:

$$R_0 = \beta\beta_M\alpha_M^2 V^* M^*/\mu_M(\alpha_M M^* + \mu_N) > 1$$

Simplifying, invasion by the spirochete requires:

$$(\beta\beta_M)\alpha_M V^* > \mu_M\left[1 + \frac{\mu_N}{\alpha_M M^*}\right] \tag{19}$$

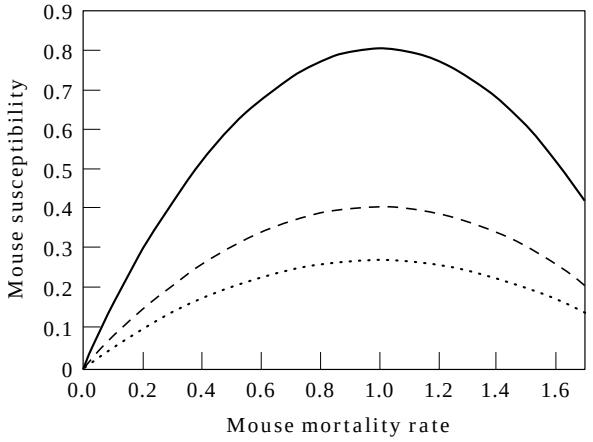

FIG. 4. Result of invasability analysis. Each curve separates (μ_M, β_M)-space into a region (above the curve) where the spirochete can invade and [m^* n^* a^*] > 0 is locally stable, and a region (below the curve) where the spirochete cannot invade. Each curve corresponds to a different tick-susceptibility probability (β); $\beta = 0.3$ (——), $\beta = 0.6$ (– – –), and $\beta = 0.9$ (.....). Parameter values are $H^* = 500$, $\alpha_H = 0.05$, $f = 600$, $\alpha_M = 0.02$, $\gamma P = 500$, $\mu_V = 0.7$, $\mu_N = 0.8$, $K_M = 20\,000$, and $r_M = 2$.

The infection will advance when rare if the number of larvae is large, if the number of mice is large (so that the initially infected nymph is likely to infect a mouse before it dies), if the geometric mean of the susceptibilities (β and β_M) is large, and if the mortality rate among mice is low. Not surprisingly, a high mortality rate among tick nymphs makes the initial advance of the spirochete infection less likely.

We rewrite the invasability condition by using eqn (9) to replace V^* in (19). The pathogen advances when rare if:

$$\frac{\mu_M}{\mu_A A^*}\left[M^* + \frac{D'}{\alpha_M}\right] < \beta\beta_M$$

Using eqn (10), the criterion for pathogen invasion becomes:

$$N^*\left[\frac{\beta\beta_M\alpha_M}{\mu_M}\right] > 1 + \frac{D'}{\alpha_M M^*} \tag{20}$$

This version of the invasability condition suggests that the spirochete's advance is promoted by a high density of nymphs, and by a high ratio of larval attacks on mice to larval attacks on alternate hosts. The latter point simply means that juvenile ticks' use of reservoir-incompetent hosts, or hosts less reservoir competent than mice, can retard the spread of *Borrelia* (Van Buskirk & Ostfeld, 1995).

If we can assume that spirochete transmission is highly efficient, then $\beta\beta_M \approx 1$. If we then neglect alternate hosts for larvae ($D' \to 0$), we reduce the invasability criterion to:

$$(1/\mu_M) > (1/\alpha_M N^*)$$

which requires only that the expected length of a mouse's life exceeds the average waiting time until the mouse is bitten by a nymph.

5. Stability

The assumption of self-regulation allows us to consider the local stability of the total population sizes separately from the stability of the numbers of infected organisms (e.g. Beretta & Takeuchi, 1995). Deer and mouse populations remain at [H^* M^*].

The Jacobian for the numbers of tick larvae, nymphs and adults is $\mathcal{J}_1$, with elements j_{ik}. We

evaluate the matrix at the equilibrium points $[V\ N\ A] = 0$ and $[V^*\ N^*\ A^*] > 0$. Then:

$$\mathscr{J}_1 = \begin{bmatrix} -(\alpha_M M^* + \mu_V + D') & 0 & \alpha_H f H^* - 2cA \\ \alpha_M M^* + D' & -(\alpha_M M^* + \mu_N + \gamma P) & 0 \\ 0 & \alpha_M M^* & -\mu_A \end{bmatrix} \tag{21}$$

H^* and M^* remain fixed and A, in $j_{13}(A)$, equals either 0 or A^*.

The stability analysis (see Appendix A) shows that extinction is unstable whenever positive equilibrium abundances are feasible. That is, if the number of deer is large enough to satisfy inequality (11), then $A^* > 0$ and extinction cannot be stable. When the positive equilibrium exists, it will be locally stable unless the ticks' intrinsic rate of increase $\alpha_H f$ exceeds a critical value. The critical $\alpha_H f$, given in Appendix A, depends on H^* and M^*. Figure 3 shows how the critical $\alpha_H f$ decreases as either H^* or M^* increases. Biologically, the ticks require sufficient deer and mouse populations to persist. But as either or both deer and mouse population sizes continue to increase, the abundance of the various tick stages can be destabilized.

Next we consider local stability of the numbers of infected organisms. The Jacobian for the numbers of infected mice, nymphs and adult ticks is $\mathscr{J}_2$, with elements ${}_2j_{ik}$. We evaluate the matrix at the equilibrium points $[m\ n\ a] = 0$ and $[m^*\ n^*\ a^*] > 0$. H, M, V, N, and A (deer, total mice and total ticks) are assumed at positive equilibrium. Then:

$$\mathscr{J}_2 = \begin{bmatrix} -(\alpha_M \beta_M n^* + \mu_M) & \alpha_M \beta_M (M^* - m^*) & 0 \\ \beta \alpha_M V^* & -(\alpha_M M^* + \mu_N + \gamma P) & 0 \\ \beta \alpha_M (N^* - n^*) & \alpha_M (M^* - \beta m^*) & -\mu_A \end{bmatrix} \tag{22}$$

The model counts infected adults because this measure is available in some field data. If $[m^*\ n^*]$ is positive and stable, so is $[m^*\ n^*\ a^*]$. Note that ${}_2j_{13} = {}_2j_{23} = 0$; the density of infected adults does not influence the dynamics of the number of infected mice or infected nymphs. a^* simply combines m^* and n^*, so we can address stability by considering $[m^*\ n^*]$; the analysis is presented in Appendix B.

First we apply the result of Appendix B to the extinction equilibrium $[m\ n\ a] = 0$. Extinction of infection (i.e. disappearance of the spirochete) is locally stable when:

$$\mu_M / M^* > \beta \alpha_m^2 \beta_M V^* / (\alpha_M M^* + \mu_N + \gamma P) \tag{23}$$

Intuitively, extinction of the spirochete infection is promoted by high mortality rates in both mice and tick nymphs, by decreased density of tick larvae, by low geometric-mean susceptibility to spirochete infection, and by low attack rates of questing ticks on mice.

If we can neglect human contacts when the spirochete initially appears, we can let $\gamma P = 0$. Then, reversing the condition for stability of the pathogen's extinction yields, after rearrangement:

$$(\beta \beta_M) \alpha_M V^* > \mu_M \left[1 + \frac{\mu_N}{\alpha_M M^*} \right]$$

This last expression recovers inequality (19), the invasability condition noted above.

Next consider the positive equilibrium $[m^*\ n^*\ a^*] > 0$. Substituting for m^* and n^* and then reducing expression (B.3) yields the condition for stability of the positive equilibrium:

$$\mu_M / M^* < \beta \alpha_M^2 \beta_M V^* / (\alpha_M M^* + \mu_N + \gamma P) \tag{24}$$

which simply reverses inequality (23). Stability of the spirochete infection at positive equilibrium is promoted by a large mouse population with low individual mortality, high geometric-mean susceptibility to the infection, a high attack rate of questing ticks on mice, by low mortality among tick nymphs, and by a high density of larval ticks. At very low densities of total tick larvae and total mice, extinction of the spirochete infection may be stable. But eradication of the spirochete would, under homogeneous mixing, require near eradication of the tick.

Figure 4 shows how the stability of the spirochete infection, hence its ability to invade an equilibrium host population, can depend on the per-individual mortality rate among mice (μ_M) and mouse susceptibility to infection (β_M). The curve separating the (μ_M, β_M)-space according to the local stability of $[m^*\ n^*$

a^*] is shown for three values of a juvenile tick's susceptibility to infection (β). For any level of μ_M, with $M^* > 0$, the likelihood of successful spirochete invasion increases as either susceptibility probability increases. A very low level of mouse mortality obviously increases the chance of successful spirochete invasion. As mouse mortality increases sufficiently, the minimal β_M required for spirochete invasion actually begins to decrease. The increase in μ_M causes a decline in M^*, which slows down the developmental advance of juvenile ticks. V^* consequently increases (see Fig. 1), and the likelihood of the positive infection equilibrium's local stability increases.

6. Discussion

We briefly evaluate some of our model's assumptions in light of alternatives. We assumed that mice do not recover from *Borrelia* infection. De Boer *et al*. (1993) found that an infected mouse may lose the spirochete if the mouse survives a near-freezing period of winter weather. But unless the mouse recovers with immunity, it could then be reinfected by a nymph carrying the spirochete, returning the mouse to the enzootic cycle of Lyme.

We assumed no transplacental transmission in mice, and no transovarial transmission in ticks. These assumptions may be reasonable for the Lyme phenomenon in the northeastern United States (Burgess *et al*., 1993). However, vertical transmission of the spirochete may occur in other *Borrelia*–tick–vertebrate interactions (Lane *et al*., 1991; Bennett, 1995). We took our assumption of no transovarial transmission to imply that all questing larvae are susceptible. But suppose that as many as 1% of questing larvae are infected (Piesman, 1993), due either to vertical transmission or to being groomed from an infectious mouse after taking only a partial blood meal (Hazler & Ostfeld, 1995). Infectious larvae could be important in the regional advance of the pathogen. Larvae sometimes attack hosts other than mice (recall the definition of D' in our model); alternate hosts include migratory birds (e.g. Ginsberg, 1993). The spirochete may be dispersed locally by mice, and transported over distances between established tick populations by birds carrying an infectious larva. But new tick populations are more likely initiated through dispersal by deer. An individual deer may carry well over 100 adult ticks (Wilson *et al*., 1990). Hence a single dispersing deer might be sufficient to establish a local tick population. As pointed out by D. Fish (pers. comm.), it is important to treat the geographic spread of the deer tick separately from the advance of *Borrelia*, since different processes are likely to be involved.

Our model ignores pathogen transmission through secondary hosts. We assume that infection of both mice and ticks occurs according to mass-action; the rates of new infection are directly proportional to the product of susceptible and infectious organisms. Most models for the dynamics of disease, and many models for host–parasite interactions, have used the same assumption (see Heesterbeek & Roberts, 1995). Hochberg (1991) considers an alternative where the densities of both susceptibles and infectives independently affect the per-individual rate of transmission. Anderson & May (1992) categorize several alternatives to mass-action according to associated biological mechanisms. Mass-action offers a simple approximation to reality, especially near equilibrium, but field data can suggest more complicated processes (D'Amico *et al*., 1996; Dwyer *et al*., 1997).

The dynamics of vector-borne disease have long been treated as distinct from most processes of direct infection transmission (see Antonovics *et al*., 1995). Ross' (1911) early model for malaria analysed the extent of infection in both a human and a mosquito-vector population; the results indicate that persistence of the disease requires a sufficient density of vectors (see Bailey, 1982). Some recent models for vector-borne disease (e.g. Thrall *et al*., 1995) assume that the number of hosts contacted per vector will increase less than linearly as host density increases. A plausible consequence is that rates of new infection should depend on the frequency of infected hosts, rather than their density.

A major difference between our model and these more general models for vector-borne disease follows from the life cycle of the deer tick. Juvenile ticks advance developmentally by feeding on mice (or other small mammals), but adult ticks reproduce after feeding on deer. The biogeography of Lyme disease in the northeastern U.S., and presumably any further advance of the disease, clearly involves patterns in tick, mouse and deer populations (e.g. Ginsberg, 1993).

Our analytical results accord reasonably well with Van Buskirk & Ostfeld's (1995) computational model for Lyme disease. Both models fix the size of vertebrate host populations and assume that the tick population self-regulates. Van Buskirk & Ostfeld (1995) constrain both the maximal number of juvenile ticks per small mammal and the maximal number of adult ticks per deer. Competition among juveniles increases their mortality, and competition among adults reduces average individual reproductive success. When one group's host(s) becomes limiting, tick

population growth becomes independent of the other host's density. Our model assumes a less mechanistic self-regulation. We let the number of larvae produced per adult decrease linearly as the size of the adult population increases. Our assumption permits some analytical results, but the processes governing tick population dynamics are not yet well understood (e.g. White *et al*., 1991).

Our model offers a simple formulation of the four-species community associated with Lyme and presents a framework for further analysis of within-habitat processes that might affect local patterns in Lyme disease. Several of the model's results follow intuitively from the assumed self-regulation and the links between spirochete infection and tick development. The model lets deer and mice combine to limit numbers of each tick stage when both hosts are rare. When both vertebrates are abundant, increasing the number of mice can decrease the number of larvae and nymphs, while still increasing the number of adults at equilibrium. Both juvenile tick stages can reach maximal density at intermediate levels of mouse abundance when deer are rare. The number of adult ticks increases with deer abundance at a rate essentially independent of the number of mice. These results assume equilibrium population sizes. The significance of dynamic equilibria for understanding the Lyme phenomenon will depend on a better understanding of population regulation in both ticks and mice.

The risk of Lyme disease in humans presumably increases with the density of infected nymphs. In our model the positive equilibrium abundance of infected nymphs increases with both larval tick abundance and the product of the mouse and tick susceptibilities to spirochete infection. Infected nymph abundance ordinarily is maximal where the total number of nymphs is greatest. As mice become more abundant, the number of nymphs begins to decline. But the increase in mice enhances the enzootic cycle. Consequently, the frequency of infection among nymphs increases, and the risk of Lyme disease fails to decline as fast as the count of total nymphs.

Parameter values in our model might be adjusted to investigate possible effects of methods proposed for controlling Lyme disease at the within-habitat scale. Lyme disease is transmitted by infectious nymphs, but management practices might focus on other tick stages (Barbour & Fish, 1993) or the vertebrate hosts (Van Buskirk & Ostfeld, 1995). The most common control measure is spraying pesticides on the ground, to elevate juvenile mortality rates μ_V and μ_N. As of this date, field tests of a device for dusting deer with insecticide are planned (D.J. White, pers. comm.). Deer are to be attracted to a bait station. When a deer attempts to feed, insecticide will be transferred mechanically to the animal's neck and shoulders, locations preferred by adult ticks. This measure might significantly increase the adult mortality rate μ_A, if enough deer can be attracted sufficiently often. Controlling Lyme disease by manipulating vertebrate-host populations (e.g. Daniels *et al*., 1993) would likely prove difficult. Our model indicates that relatively small populations of deer and mice can support high equilibrium densities of questing, infectious nymphs. Furthermore, the model suggests that reducing mouse density from high to moderate might increase the positive equilibrium abundance of infectious nymphs, depending on the resulting rate at which nymphs become adults by attacking mice. Van Buskirk & Ostfeld (1995) conclude that habitat alterations reducing the number of mice and increasing the number of alternate (less reservoir competent) hosts for juvenile ticks might reduce the risk of Lyme disease.

Our primary focus is the pathogen's invasion of a host community. Controlling the spread of Lyme disease at the periphery of the spirochete's range might be easier than decreasing incidence in areas where the disease is endemic. The spirochete's advance when rare becomes less likely if the density of susceptible mice is decreased, or the density of alternate hosts is increased. Pathogen invasion of a host community might be impeded by immunizing mice against Lyme (D.J. White, pers. comm.). Vaccine might be mixed with food, and the mixture left in areas where mice occur at high density. Immunized mice would still be attacked by juvenile ticks, but would be removed from the enzootic cycle of infection. For additional discussion, see Bennett (1995) or Van Buskirk & Ostfeld (1995).

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APPENDIX A

Using expression (21), we set Det $[\mathscr{J}_1 - \lambda I] = 0$ and obtain the characteristic equation:

$$\lambda^3 + \lambda^2(-[j_{11} + j_{22} + j_{33}]) + \lambda(j_{11}j_{22} + j_{22}j_{33} + j_{11}j_{33}) - (j_{11}j_{22}j_{33}) - j_{21}j_{32}[j_{13}(A)] = 0 \qquad \text{(A.1)}$$

Local stability, by the Routh–Hurwitz method, requires:

(1) $-(j_{11} + j_{22} + j_{33}) > 0$
(2) $-(j_{11}j_{22}j_{33}) - j_{21}j_{32}[j_{13}(A)] > 0$
(3) $-(j_{11} + j_{22} + j_{33})(j_{11}j_{22} + j_{22}j_{33} + j_{11}j_{33}) > -(j_{11}j_{22}j_{33}) - j_{21}j_{32}[j_{13}(A)]$

Since $j_{ii} < 0$ for $i = 1$, 2 and 3, condition (1) is true by inspection. If condition (2) holds, then:

$$-\frac{j_{11}j_{22}j_{33}}{j_{21}j_{32}} > j_{13}(A) = \alpha_H f H^* - 2cA \qquad \text{(A.2)}$$

Substituting and rearranging yields:

$$A > \frac{\alpha_H f H^*}{2c} - \frac{(\alpha_M M^* + \mu_V + D')(\alpha_M M^* + \mu_N + \gamma P)\mu_A}{2c\alpha_M M^*(\alpha_M M^* + D')} \qquad \text{(A.3)}$$

The right-hand side of expression (A.3) is simply $A^*/2$; see eqn (8). Hence condition (2) becomes $A > A^*/2$. This cannot be true at the extinction equilibrium; hence extinction is unstable when A^* is feasible. But condition (2) must be true if the adult equilibrium is positive.

To analyze (3), let $\sigma = (j_{11}j_{22} + j_{22}j_{33} + j_{11}j_{33})$, let $r = \alpha_H f$, and let $b = -(j_{11}j_{22}j_{33})/(j_{21}j_{32}) > 0$. Then, from eqn (8), $A^* = (r/c)H^* - (b/c)$. Then $j_{13}(A^*)$ becomes $(2b - rH^*)$, and condition (3) becomes:

$$-(j_{11} + j_{22} + j_{33}) + \sigma > -(j_{11}j_{22}j_{33}) - j_{21}j_{32}(2b - rH^*)$$

Condition (3) should hold when rH^* is not too large, but can fail despite the requirement that the maximal value of H^* varies inversely with r (insuring $F_V > 0$). Rearranging, $[V^*\ N^*\ A^*] > 0$ is locally stable if:

$$r < \frac{b}{H^*} + \frac{\sigma - (j_{11} + j_{22} + j_{33})}{H^* j_{21}j_{32}} \qquad \text{(A.4)}$$

APPENDIX B

The interaction of infected mice and infected nymphs has Jacobian $\mathscr{J}'$, a sub-matrix of $\mathscr{J}_2$:

$$\mathscr{J}' = \begin{bmatrix} -(\alpha_M\beta_M n^* + \mu_M) & \alpha_M\beta_M(M^* - m^*) \\ \beta\alpha_M V^* & -(\alpha_M M^* + \mu_N + \gamma P) \end{bmatrix} \qquad \text{(B.1)}$$

We represent the elements of $\mathscr{J}'$ by j'_{ik}. By column expansion, Det $\mathscr{J}_2 = -\mu_A$ Det $\mathscr{J}'$, since stability depends on the infected mouse–nymph interaction. $|\mathscr{J}' - \lambda I| = 0$ yields:

$$\lambda^2 - (j'_{11} + j'_{22})\lambda + (j'_{11}j'_{22} - j'_{12}j'_{21}) = 0 \qquad \text{(B.2)}$$

Local stability requires:

(1) $-(j'_{11} + j'_{22}) > 0$
(2) $j'_{11}j'_{22} - j'_{12}j'_{21} > 0$

Since $j'_{ii} < 0$ for $i = 1$ and 2, condition (1) is true by inspection. If condition (2) holds, then:

$$(\alpha_M\beta_M n^* + \mu_M)(\alpha_M M^* + \mu_N + \gamma P) > \beta\alpha_M^2\beta_M V^*(M^* - m^*) \qquad \text{(B.3)}$$

for local stability of the infection equilibrium. Expression (B.3) is applied in the text.