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A geographical perspective of virulence

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1. INTRODUCTION

The work of Anderson and May led the way in establishing that parasitic organisms had the potential to drive the population dynamics of their hosts. Since their seminal work in the late 1970s and early 1980s, there has been an explosion of research aimed at understanding and applying the diverse ecological and evolutionary dynamics produced by relatively simple models of infectious disease (Chapters in this book).

The parasite flagship is the notion of 'virulence'. Understanding variation in virulence has proved a rewarding intellectual endeavour, and will likely be valuable in the control of infectious disease (Dieckmann et al. 2000). This chapter is about virulence and its evolution. We have three goals. First, we wish to continue the ongoing discussion of the notion of 'virulence'. We take an individual genotype approach distinguishing two types of virulence. We discuss some complexities and shortcomings of this simple classification.

Much of this chapter is dedicated to our second objective, that being to discover how to expect the two types of virulence to vary over spatial gradients in host productivity. If environmental differences over geographical ranges do influence the adaptiveness of virulence, then it should come as little surprise that spatio-temporal variation in environments could lead to spatio-temporal variation in virulence. Host-parasite interactions may vary over (1) local scales, where population distributions may be heterogeneous, (2) regional scales, where the flow individuals from patch to patch may be restricted, and any spatial structure is likely to be influenced by a combination of local dynamics and regional movement, and (3) geographic scales, in which individual flows may be minute or non-existent, and the biotic and abiotic environments extrinsic to the host-parasite association are likely to play roles in pattern formation. This chapter will mostly concern the latter of these three scales, although we will make reference to studies best situated in the first two of these scales.

Finally, we discuss our findings in relation to previous experimental studies. It transpires that it is much too early to confront theory with data, and so we make a series of predictions which we believe, if tested experimentally or expanded theoretically, should yield a wealth of insights into a geographic theory of host-parasite interactions.

2. FACETS OF VIRULENCE AND SELECTION

2.1. Type 1 and Type 2 Virulence

'Virulence' is used in a variety of ways in the literature, and can have (sometimes subtly) different meanings depending on the specific questions addressed and variables measured. For example, a plant pathologist often equates virulence with the capacity of a given parasite strain to infect an individual plant. A parasitoid biologist by contrast may refer to virulence as the capacity of a parasitoid larva to develop to maturity within its host. Finally, an epidemiologist equates virulence with morbidity (i.e., sickness) and/or mortality of infected hosts.

In this chapter, we employ "Type 1 virulence" to mean the *compatibility* of a parasite genotype (or species) for a specific host genotype (or species) over the sequential steps of the interaction. The sequences can be roughly broken down into infection of, development within, and transmission from the host. Each sequential step involves evasion or manipulation of the host's systems of reconnaissance and defence. Type 1 virulence is therefore a set of probability measures of parasite fitness whilst in contact with its host.

Contrast this with "Type 2 virulence" which is used to mean genotype x genotype *effects* of an infection on host fitness. Effects may arise as an indirect or direct consequence of Type 1 virulence, that is the exploitation strategy employed by the parasite, or by mismatching of host and parasite genotypes. Fitness consequences for the host are usually measured as increased probabilities of mortality of potentially reproducing hosts (the classical view) and/or reduced levels of reproduction (Ebert 1998), but they may also entail more subtle changes in fitness via alterations in host life-histories (e.g., Agnew et al. 1999 and references therein) and host homeostasis (e.g. host physiology and/or behaviour). In this chapter, we will be mostly interested in Type 2 virulence.

2.2. A canonical model

In much of what follows, consider the following modification of the standard susceptible-infected model (Anderson and May 1981; Hochberg 1991):

$$dS/dt = (a - b - \theta N - \beta I - \theta_S'\{I,S\})\, S + ((1 - \tau)(a - a') + \gamma)\, I , \quad (1a)$$

$$dI/dt = [\beta S + \tau (a - a') - (b + \alpha + \gamma) - \theta N - \theta_I'\{I,S\}]\, I , \quad (1b)$$

$$dN/dt = (a-b-\theta N)\, N - [(a'+\alpha+\theta_I'\{I,S\})]\, I - \theta_S'\{I,S\}\, S , \quad (1c)$$

where S is susceptible density, I is infected density, and N is total density (S+I). a is the per capita birth rate and b the per capita death rate of hosts, β is the transmission constant, and γ is the recovery rate. The parameter a' is the reduction in host birth rate, and α the added mortality, due to the parasite. τ is the efficiency of vertical transmission. The parameter θ describes intrinsic host density dependence, and the functions $\theta_i'\{S,I\}$ reflect aggravated effects of the parasite associated with host densities (Anderson and May 1981; Hochberg 1991). Any of the parameters in the second pair of square brackets of eqn. (1c) could be modified to include consequences of between-host distributions of parasite loads (Anderson and May 1978; Anderson 1979; Rousset *et al*. 1996).

2.3. Type 1 virulence

The ecological model presented in equation (1) does not easily lend itself to interpretations regarding Type 1 virulence. What would be necessary is to expand the model to multiple host and parasite genotypes and consider the probabilities of infection, within-host development, and the liberation of infectious parasites for subsequent horizontal transmission (or mobilisation for vertical transmission). Each of these qualitatively different sequential steps may be broken down further into probability sequences (Hochberg 1998). The full sequence begins with the initiation of the infection process (step 1) and ends with the decoupling of host and parasite (step n). Symbolically, Type 1 virulence (or $V_{1,k}$) of the k^{th} step in the interaction between a particular host type and particular parasite type is

$$V_{1,k} = P\{k\} , \qquad (2)$$

where $P\{k\}$ is the probability of the k^{th} step occurring. Thus, Type 1 virulence is a set of interaction probabilities, which may or may not correlate with one another.

2.4. Type 2 virulence

Type 2 virulence (denoted V_2) is the negative effects of parasitism on per capita infected host growth rate. This is given by the terms in the second pair of brackets of equation (1)

$$V_2 = a' + \alpha + \theta_I'\{I,S\} . \qquad (3)$$

Like for Type 1 virulence, this index would be more complex if it were based on a more realistic model incorporating heterogeneous distributions of parasite numbers and genotypes over the infected host population. If $V_2<0$ then the infectious agent has a net beneficial impact on the host.

Distinguish V_2 from the per capita negative effect of the parasite on the whole host population, or the *epidemiological impact*

$$\psi = V_2 I + \theta_S'\{I,S\} S = -dN/dt + (a - b - \theta N)N . \qquad (4)$$

For the parasite to be a parasite, V_2 and ψ must both be positive, although some components may be negative (e.g., the parasite may induce infected hosts to produce more offspring than healthy hosts ($a'<0$), or infecteds may be quarantined, and hence not compete ($\theta_I'<0$)). Some parameters have much more latitude to affect V_2 (and therefore ψ) than others. For example, a' has an upper bound of a, whereas α has no upper bound in this model. Because of the multitude of feedbacks in model, it is difficult without formal analysis of explicit models to know how V_2 and ψ will dynamically covary.

Given that parasites may have impacts on healthy hosts (via aggressivity of infecteds, or costs paid in caring for infecteds) without actually infecting them, V_2 and ψ highlight the extended phenotype (*sensu* Dawkins 1982) aspect of selection: the demographic consequences of the parasite involve more than just their direct effects on infected hosts. If indeed, as suggested here, competition is aggravated by parasites, then the life-style of what are potentially the most Type 2 virulent

parasites are castrators (see chapter by Kuris and Lafferty). This is because the parasite (1) severely reduces or eliminates the reproductive output of its host and (2) the infected host (often larger as a consequence of castration) may differentially compete with other, related hosts, thereby reinforcing the epidemiological impacts of single infections on given host genotypes.

Transmissibility and recovery (and therefore V_1) can have hidden effects on V_2 and ψ, in that they may influence susceptible and infected host densities (i.e., if $\theta' \neq 0$). Notice that it is not clear (i.e., without specifying θ') whether higher Type 2 virulence will increase or decrease Type 1 virulence and/or selection; the direction(s) of the effect on one or both of these indices depend(s) on the marginal effects of their increase on the complex quantity θ'. Moreover, if densities S and/or I vary through time, it is conceivable that marginal increases in Type 1 virulence may increase Type 2 virulence and/or selection at certain times or places, and decrease one or both of them in others. This problem merits more concerted research.

3. PATTERNS IN VIRULENCE ALONG PRODUCTIVITY GRADIENTS

What is now emerging as a geographical theory of virulence has its roots in the more general framework of the geographical theory of coevolution (Thompson 1994, 1999). The two basic components of a geographical theory of virulence are (1) the biology of focal host-parasite associations and (2) the template over which the interaction occurs. The biology of the association depends on genotypic and phenotypic effects on the expression of virulence. Population biology is played-out over the geographic template, which integrates the distributions of habitat productivities (see below), habitat sizes, inter-habitat distances, and habitat configuration (i.e., which patch is next to which). Biology and template are linked by host and parasite behaviour (i.e. historical and/or current migration and dispersal), creating the emergent properties of adaptation (Gandon et al. 1996; Hochberg and van Baalen 1998; Nuismer et al. 1999; Parker 1999; Gomulkiewicz et al. accepted). The model presented below examines variation in a single component of this theory—habitat productivity.

The question posed here is thus how does habitat productivity affect the persistence of different types of host-symbiont association, creating with it patterns in Type 2 virulence?

3.1. A model of competition between host-symbiont pairs

We present a model of symbiont-host associations that illustrates how competition can play itself out over geographical gradients in habitat suitability (see also Hochberg et al. 2000). The model can be interpreted as two symbiont types competing for a single host type or a single symbiont infecting two competing host types. The biologies of both host and symbionts are extremely simple: (1) all hosts are infected by one and at most one symbiont, (2) the populations exhibit continuous and overlapping generation structure, (3) the 'types' are assumed to be clones of a single species, (4) mutation and migration are at low enough levels so as not to affect population densities, but are sufficient to maintain all populations in all habitats, and (5) the host is always limited to some extent by its own density (due to the effects of resource limitation).

Host-symbiont pairings are of density N_1 and N_2, and the total population density is thus $N= N_1+N_2$. Habitat productivity is defined as the growth rate of the host population in the absence of symbionts (the notion of 'productivity' employed here should be differentiated from individual host 'condition', although the two may be interrelated). Specifically, independent of any symbiont effect, the birth rate of the host is a_U and death rate b. Hosts experience interference competition, with their densities being limited jointly and uniformly by a logistic-type model with rate constant q (see also Hernandez 1998). Therefore, habitat productivity is encapsulated in three quantities a_U, b and q, each of which may vary across the host's geographical range. Productivity increases with a_U and decreases with b and q.

The symbiont has density independent and density dependent effects on its host. Net host reproduction is increased by rates a_1 and a_2. Pathogenic effects of a particular pairing type on the host increase the background death rate (b) for pairings 1 and 2 by α_1 and α_2, respectively. Finally, direct competition may be alleviated or intensified by the symbiont, with c_1 and c_2 the impacts of harbouring symbionts on host-host competition. When $c>0$ the symbiont intensifies competition whereas when $c<0$ it alleviates it. It is assumed as a constraint that $c>-q$, that is the symbiont cannot reverse density dependence. Finally, host-symbiont pairs compete by what we call 'expansion competition', whereby the superior competing couple gain resources at the expense of the inferior competing couple (cf. link with intraguild predation, Hochberg and Holt 1990). Thus, in the model presented below the parameter δ is the net rate (positive or negative) at which pairing 2 becomes pairing 1. An example of this is cross-transmission, or the horizontal transmission of, and competition between, two parasite strains or species (e.g., Mosquera and Adler 1998).

The differential equations describing the per capita changes for pairings 1 and 2 are:

$$dN_1/N_1dt = [r_U - qN] + [r_1 - c_1N] + \delta N_2 \quad (5a)$$

$$dN_2/N_2dt = [r_U - qN] + [r_2 - c_2N] - \delta N_1 \quad (5b)$$

where $r_U=a_U-b$, $r_1=a_1-\alpha_1$ and $r_2=a_2-\alpha_2$. The quantity r_U is the per capita rate of increase of hosts independent of symbiosis, and r_1 and r_2 are the respective effects of virulent and avirulent pairings on per capita host growth rate.

Model equations (5) albeit simple biologically illustrate the complexity of the notion of Type 2 virulence. The classical effects are encapsulated in the per capita terms r_i (Hochberg 1998; Ebert 1998). However, harbouring a symbiont may have repercussions for both the intra- and interspecfic pairings. Thus in this model, the Type 2 virulence of coupling *i* (*i*=1,2) when potentially competing with coupling *j* (*j*=1,2) is given by the second terms in brackets, or

$$V_{2i} = -(r_i - c_i (N_1+N_2)) \quad (6)$$

This means that the more virulent pairing will depend upon both constant parameters and population densities. It is interesting in this respect that other purely ecological factors (e.g. competition with other species, other natural enemies, etc.) impinging on N can potentially effect what we perceive as Type 2 virulence. Note that if the notion of Type 2 virulence were extended to

more of a community context, then it would be necessary to include model terms reflecting expansion competition (e.g., δ), thereby blurring the notion of Type 2 virulence.

3.2. Results

3.2.1. Ecology

If a single pairing persists on its own, it does so at an equilibrium density of

$$N_I^* = (r_U + r_i) / (q + c_i) . \quad (7)$$

Note that the coupling can only persist in a habitat sink ($r_U<0$) if the effect of the symbiont on the host is sufficiently positive that is $r_i>-r_U$, that is a mutualist (Hochberg et al. 2000).

Substituting (7) into (6) gives

$$V_{2i} = (c_i r_U - r_i q) / (q + c_i) . \quad (8)$$

The effects of habitat quality on virulence are the same regardless of which habitat quality parameter is under consideration (r_U or q). Increasing habitat quality increases virulence as long as the symbiont intensifies the effects of competition (i.e. $c_i>0$), whereas virulence decreases with quality if the symbiont reduces the effects of competition (i.e. $c_i<0$). It can easily be seen from (8) that if $r_U c_i<r_i q$ then the symbiont is a mutualist (i.e., $V_2<0$), whereas if this inequality is reversed, then it is a parasite.

3.2.2. Outcome of competition between symbiont pairs

What is the effect of habitat on two competing host-symbiont pairs? As shown below, the fate of the two population system depends on habitat productivity (parameters r_U and q), expansion competition (δ), symbiont effect on host competition (c_i), and symbiont effect on per capita growth (r_i).

First consider a situation where expansion competition is virtually nil (i.e., $\delta\approx0$). If the symbiont pairing *i* is less virulent over all possible densities than coupling *j* (i.e. $r_i>r_j$ and $c_i<c_j$), then the former competitively eliminates the more virulent coupling regardless of habitat quality. If in contrast $r_i>r_j$ and $c_i>c_j$ then the protector coupling *j* prevails when habitat quality is sufficient or

$$r_U > [r_i (q+c_j) - r_j (q+c_i)] / (c_i-c_j) , \quad (9)$$

whereas the provider coupling prevails in more marginal habitats (i.e. when the inequality is reversed). Therefore, to obtain coexistence between genotypes in space as a function of habitat quality, the provider must have a higher growth rate than the protector at low habitat qualities and a lower growth rate in habitats of high quality. The density independent component of virulence plays against more virulent associations in marginal habitats (with *i* the victor), whereas the density dependent component acts in productive habitats (with *j* the victor).

Now consider the scenario of expansion competition between pairings. Hochberg et al. (2000) showed that a relatively virulent symbiont can persist in the face of a less virulent competitor if the former is the better cross-transmitter; otherwise the relatively avirulent symbiont prevails in all habitats where it can persist on its own with the host. As explained in Hochberg et al. (2000), the better cross-transmitter has an overall competitive advantage as habitat productivity increases. However, their model did not consider the possibility that symbionts could affect the fitness of their hosts differentially as a function of host-host competition (i.e. $c_i=c_j=0$ in their model). The major influence of adding expansion competition is that the better competitor will tend to increase the range of productive habitats it can occupy. Thus, consider four scenarios.

1. **Pairing *i* is better at provision, protection and cross-transmission ($r_i>r_j$, $c_i<c_j$, $\delta>0$).** The simple result is that pairing *i* competitively eliminates pairing *j* for any habitat quality where persistence is possible. Type 2 virulence follows expression 8.

2. **Pairing *i* is better at provision and protection, but pairing *j* dominates cross-transmission ($r_i>r_j$, $c_i<c_j$, $\delta<0$).** Here, pairing *j* can only persist in habitats of sufficient productivity, and only if $\delta<c_i-c_j$; that is, the advantage of pairing *j* at cross-transmission must exceed the differential amount protection found in pairing *i* compared to pairing *j*. Pairing *j* always expresses higher Type 2 virulence than pairing *i* meaning that we should expect to observe more virulent interactions in productive habitats.

3. **Pairing *i* is the better provider, and pairing *j* is best at protection and cross-transmission ($r_i>r_j$, $c_i>c_j$, $\delta<0$).** The result is that pairing *j* persists in habitats of sufficiently high productivity $r_U>(r_i(\delta+q+c_j)-r_j(q+c_i))/(c_i-c_j-\delta)$, and its Type 2 virulence is given by equation 8.

4. **Pairing *i* is the better protector, and pairing *j* is better at provision and cross-transmission ($r_i<r_j$, $c_i<c_j$, $\delta<0$).** Here, a competitive advantage is rendered to pairing *j* in productive environments meaning that providers should tend to encroach on protectors.

3.2.3. An ESS approach

Studying the outcome of competition between two strains of symbionts gives many insights into the selective factors. However, it gives only limited insight into the eventual evolutionary outcome, as many other strains are possible. To approach the problem of optimisation, the concept of evolutionarily stable strategy or ESS (Maynard Smith and Price 1973) becomes useful. To find a potential ESS, we need to determine whether any arbitrary mutant will invade. If no mutant has positive invasion fitness, then the resident is evolutionarily stable.

How can a mutant symbiont strain increase its invasion fitness? Consider the model presented by equations (5a) and (5b). To derive the invasion conditions, we have to be more specific about how the expansion parameter δ depends on the traits of competing symbiont strains.

For a symbiont to expand, its host should be 'infective' and the recipient host 'susceptible'. Let the infectivity of a symbiont i be given by β_i so that the force of infection of symbiont strain is $\beta_i N_i$. The symbionts of the recipient host may be able to resist the invading symbiont, so that only

a proportion σ_i of the super-infection attempts is successful. Then, the net of expansion of strain 1 is

$$\delta = \beta_1 \sigma_2 - \beta_2 \sigma_1 . \quad (10)$$

With this, we can represent the per-capita fitness of the two strains as

$$f_1 = (r_U - q (N_1 + N_2)) + (r_1 - c_1 (N_1 + N_2)) + (\beta_1 \sigma_2 - \beta_2 \sigma_1) N_2 \quad (11a)$$
$$f_2 = (r_U - q (N_1 + N_2)) + (r_2 - c_2 (N_1 + N_2)) + (\beta_2 \sigma_1 - \beta_1 \sigma_2) N_1 \quad (11b)$$

Assume now that strain 1 is the dominant resident strain (whose equilibrium density given by equation (7)), and strain 2 a rare mutant ($N_2 \approx 0$). At equilibrium the resident does not grow, or

$$(r_U - q N_1) + (r_1 - c_1 N_1) = 0 \quad (12)$$

and the mutant invades if its fitness is positive, or

$$(r_U - q N_1) + (r_2 - c_2 N_1) + (\beta_2 \sigma_1 - \beta_1 \sigma_2) N_1 > 0 . \quad (13)$$

Which types of mutants will be able to invade? Representing the differences between mutant and resident by Δ, we use eqns. 12 and 13 to derive the invasion condition

$$\Delta r + (- \Delta c + \Delta\beta \sigma_1 - \beta_1 \Delta\sigma) N_1 > 0 . \quad (14)$$

Thus, a mutant symbiont may invade by (i) increasing its host's rate of reproduction ($\Delta r>0$), (ii) decreasing its susceptibility to intraspecific competition ($\Delta c<0$), (iii) increasing its infectivity ($\Delta\beta>0$), or reducing the probability of take-over by another symbiont ($\Delta\sigma<0$). Which strains will invade (and which strain will ultimately resist invasion by all other strains) will depend on the trade-offs between these fitness components. These trade-offs are the result of the interaction between host individuals and symbiont clones, and will depend in complex ways on the physiology of both. Yet, qualitative predictions can be made without specifying the trade-offs in full. In particular, we can assess how the importance of the fitness components depends on the ecology of the resident host-symbiont system.

1. Under conditions where the density of the resident host-symbiont system is low, it the optimal strategy for the mutant is to boost its host's net rate of reproduction.

2. The relative importance of the other fitness components is proportional to overall host density. Therefore, if environmental productivity improves, the selective advantages of 'protection', 'expansion' and 'defence' increase.

Note that when the symbiont population is monomorphic, host take-over will not be observable. Yet it will still occur, and it is a factor that determines the ESS of the symbiont, as is revealed by the fitness function of a mutant symbiont close to the resident.

When does a symbiont change from being a mutualist into being a parasite or *vice versa*? Consider the fitness of a host in a system with two strains of symbionts. Superinfection by the two strains means that it is infected by strain 2 on average

$$\phi_2 = \beta_2 \sigma_1 N_2 / (\beta_1 \sigma_2 N_1 + \beta_2 \sigma_1 N_2) , \qquad (15)$$

so that its expected fitness is

$$\begin{aligned} f_{host} &= (r_U - q(N_1 + N_2)) + (1-\phi_2)(r_1 - c_1(N_1 + N_2)) + \phi_2(r_2 - c_2(N_1 + N_2)) \\ &= (r_U - q(N_1 + N_2)) + (r_1 - c_1(N_1 + N_2)) + \phi_2(\Delta r - \Delta c(N_1 + N_2)) \end{aligned} \qquad (16)$$

When the mutant is rare, ϕ_2 will be very small, but *if* the host is infected with the mutant, it would prefer the symbiont to increase

$$\Delta r - \Delta c\, N_1 . \qquad (17)$$

However, the mutant symbiont will maximise the left hand side of eqn. 14. Hence the overlap in interest between host and symbiont is $\Delta r - \Delta c\, N_1$, whereas the private interests of the symbionts are given by the cross-infection terms $(\Delta\beta\, \sigma_1 - \beta_1\, \Delta\sigma)\, N_1$. Since at the mutant's optimum the left hand side of eqn. 14 will be zero, we can conclude that the optimal strategy for the symbiont will serve the host's interests as well if

$$\Delta\beta\, \sigma_1 - \beta_1\, \Delta\sigma \qquad (18)$$

is negative. Hence only if the symbiont invests sufficiently in defence ($\Delta\sigma$) will it become a mutualist. If, on the other hand, it invests in expansion, it will become a net parasite. Whether it *will* become mutualistic or symbiotic depends on relative costs and benefits of expansion and defence, as well as on the trade-off with provision and protection options.

Only in absence of hosts with competing symbionts should we expect complete overlap between the interests of host and symbiont. In all other cases, the symbiont will trade some of its host's interests to boost its own expansion. This conflict is most intense at high host densities, and hence (i) in regions of highest productivity and (ii) regions where symbionts significantly boost host reproduction. In the latter case there will be a negative feedback: overlap in interest tends to increase host density, whereas conflict tends to reduce it.

4. DISCUSSION

The argument that local environment can influence the relationships between consumers and their resources, although not new, has only received concerted attention in the past few years. Some of the main studies leading up to recent explorations include the experiments of Joen (1972, 1987) and the discussions by Eberhard (1980). Coley and colleagues (1985) were one of the first to have considered the problem mathematically. They argued that slow growth rates of plants in marginal environments favoured investment in anti-herbivore defences. Loreau and de Mazancourt (1999) have recently re-explored this finding, showing that the details of model assumptions may either support or refute Coley et al.'s claims. In contrast, two recent theoretical studies indicate that virulence should be minimal in low quality environments (Type 1 virulence, Hochberg and van Baalen 1998; Type 2 virulence, Hochberg et al. 2000; Koella, submitted).

In the model developed here, poor habitats render density dependent selection unimportant, and the host-symbiont coupling with the highest intrinsic growth rate (r_i) tends to prevail. That is, avirulent Type 2 effects should dominate in the least productive environments in a species range, because these are directly linked to density independent (e.g., vertical) transmission (Hochberg et al. 2000). Contrast this with productive habitats where density dependent selection becomes important. Here, the winning pair tends to be the better one at expansion competition (highest $|\delta|$), and/or the host-symbiont pair least affected by density dependence (lowest c).

The effect of habitat productivity can be understood in terms of the conflict of interest between host and symbiont. Expansion serves the interests of the symbiont but not those of the host. This conflict will be most intense when there are many opportunities for expansion. High habitat productivity will therefore tend to intensify the host-symbiont conflict because it increases host density. At the same time, however, there may be a relation with diversity of the symbionts. In high-competition environments, symbionts may be favoured that, rather than expand, defend their hosts against infection by other strains. Such symbionts have more to gain by helping their host to reproduce. If the expanding symbionts are likely to be type 2 virulent, it is in the interest of the host to carry protecting strains. This kind of overlap will occur only in productive habitats. Host-symbiont mutualisms may therefore occur in all kinds of environments, but for different reasons.

4.1. Empirical studies

Despite an increasing body of research on spatial aspects of adaptation in host-parasite associations (Mopper and Strauss 1998), we still are in the early days of understanding why virulence varies over geographical scales. Most studies that show pattern were not designed to take habitat conditions into account (e.g., Ebert 1994; Kaltz and Shykoff 1998), and therefore cannot be compared and contrasted with the theory presented here. Below we very briefly present those studies in which some measure of habitat productivity was taken into consideration. We stress that none of these studies test the theory of habitat productivity, and so our comparisons are necessarily *ad hoc* and should be taken with appropriate caution.

4.1.1. Burdon et al. (1983) and Oates et al. (1983)

Burdon, Oates and Marshall (1983) showed that northern populations of oats (*Avena*) in more favourable (mesic) conditions were more resistant to the rust *Puccinia coronata* than populations in southern, arid environments in New South Wales, Australia. Oates, Burdon and Brouwer (1983) considered the flip-side of the interaction and showed a trend for increasing (Type 1) parasite virulence from arid to mesic sites. Assuming that the northern sites were more favourable for pathogen transmission, these results concord with theoretical predictions that exploiter (Type 1) virulence and victim resistance should both tend to increase with exploiter attack rate (Hochberg and Holt 1995; Hochberg and van Baalen 1998).

4.1.3. Bohannan and Lenski (1997)

These authors varied the level of glucose input into chemostats and monitored the population dynamics of susceptible and resistant forms of *Escherichia coli* when faced with a bateriophage. They demonstrated that (1) predation pressure, (2) the rate of appearance of mutant resistant hosts, and (3) the rate of replacement of phage-sensitive clones by resistant clones all increase with nutrient enrichment. Because the phage did not evolve in this experimental set-up, invasion of resistant bacteria resulted in the system being transformed from parasite-limitation to resource-limitation. Assuming that the exploiter does not evolve, some theoretical studies show that resistant hosts should be differentially selected in productive environments (Hochberg and Holt 1995; Hochberg and van Baalen 1998; Koella submitted), whereas others seem to suggest the opposite (Coley et al. 1985). Further theoretical investigation is needed to elucidate the factors responsible for which of the two contrasting patterns is produced (see discussions in Hochberg and van Baalen 1998; Hochberg et al. 2000; Loreau and de Mazancourt 1999).

4.1.4. Krackauer and Mira (1999)

These authors performed comparative analyses on the phenomenon of atresia: the destruction of germ cells before fertilisation. They found that species with high fecundities tend to provide more mitochondria per germ cell and that atresia differentially occurs in species providing fewer mitochondria per cell. The authors suggest that atresia serves to limit the accumulation of deleterious mutations, and that this phenomenon is more pronounced in species with low fecundities because of the pre-zygotic cost of maladaptation. Life-history models appropriate to evaluate Krackauer and Mira's finding have yet to be developed.

4.1.5. Yu and Pierce (1998)

These authors looked at the relative distributions of ants (*Allomerus* cf. *demerarae*) which protect but castrate their plants (*Cordia nodosa*) and ants which alone protect (3 species of *Azteca*). They find that the purely mutualistic species is more frequent in habitats with low densities of ant plants, whereas the protecting/castrating species is more frequent in areas of high plant density. Both ant species are 'protectors' and the model presented in this chapter predicts that a protector which comes at a cost should tend to dominate productive environments (i.e., with high plant densities) if it is the better cross-transmittor. Indeed, Yu and Pierce show that *Allomerus* is competitively dominant to *Azteca*.

4.1.6. Guegan et al (submitted)

Using data from 150 different countries, these authors examine how life-history parameters in human populations correlate with social and demographic variables. They find significant effects involving human fertility and a panoply of variables. Moreover, when they control for these significant effects, they find that the diversity of pathogenic infectious diseases over countries significantly explains variation in human fertility (although no causation between the two variables could be established). These results are broadly similar to those found by Hochberg and van Baalen (1998).

4.2. Predictions and speculations

Below, we make several testable predictions based on the productivity theory of the evolution of virulence (Hochberg and van Baalen 1998; Hochberg et al. 2000; this chapter).

4.2.1. Specialisation

A pervasive question in host-parasite interactions concerns the range of host types (e.g., clones, species) a given parasite type can exploit, and the range of parasite types a given host type can defend itself against. This problem has been evaluated in non-spatial host-parasite systems by Frank (1996), but it is difficult from his results to make spatial predictions across habitats of differing productivities. Hochberg and van Baalen (1998) looked at a gene-for-gene model of prey-predator coevolutionary relations over habitat gradients. They assumed that increasing generalisation brought with it an explicit metabolic cost, whereas the implicit cost of specialisation is being in the presence of types which cannot be exploited (for the predator) or not being able to defend against (for the prey). They found that the *potentially* most generalised predatory and prey types should occur in habitats with the highest prey productivities. However, because in their model genotypic diversity is maximal at intermediate levels of specialisation/generalisation (e.g., there is only one way to be a complete generalist, see below), the *realised* level of generalisation is greatest in habitats of intermediate productivity. In contrast, in the most marginal habitats, both species are represented by few specialists, and so both the *potential* and *realised* levels of specialisation there are high.

4.2.2. Diversity

The behaviour of this same gene-for-gene model can be interpreted in terms of how genic diversity should vary across habitat productivity gradients (see also Janssen and Mulder 1999). Assuming a wide range of environmental productivities, the Hochberg and van Baalen model predicts that the highest diversities should be maintained in environments of intermediate productivity. Encouragingly this is qualitatively what is empirically found for species diversity curves across latitudes (Rosenzweig 1995). However, caution should be taken in interpreting this accord between theory and data insofar as 'intermediate' in the model may not correspond to real levels of productivity in nature, and that the model would have to be modified if it were to consider species rather than genotypes within a species.

4.2.3. Sex

Geographic parthenogenesis is an empirical pattern where sexual species tend to be found in more productive and less disturbed habitats than asexual relatives (Ghiselin 1974). Glesener and Tilman (1978) proposed that sexual organisms should be found in areas of high biotic stress, whereas asexual counterparts should be located in areas of abiotic stress. We suggest that parasites are capable of maintaining sexual morphs of a species in the most favorable habitats for the host (see also Hochberg et al. 2000), but only when provider symbionts are of little importance along one or more productivity axes. This proposition integrates two well established theories.

First, it is well established theoretically that parasites can only persist in a host population if the latter's density is beyond a threshold level (Anderson and May 1981). The theory developed by Hochberg and van Baalen (1998) predicts that selection pressure imposed by a parasite should be increasingly intense (up to a point) as habitat suitability for the host increases. Lawton (1996) has argued that densities tend to be highest in the most productive areas for the species, and Holt *et al*. (1997) describe mechanisms generating this correlation.

Second, it has been argued that persistent coevolutionary interactions between host and parasite in suitable habitats can favour sexual morphs over asexual morphs (Ebert and Hamilton 1996), because sex is more likely to produce and maintain a range of adapted variants than is asexual reproduction. The frequency dependent cycles necessary for the maintenance of sex are not produced by the model presented in this chapter; however they can occur if the basic ecological model is modified to give unstable local dynamics, and if the co-evolutionary interaction is based on certain qualitative genetic mechanisms, such as matching alleles (Frank 1996).

4.3. Conclusion

We are still in the very early days of studies on spatial patterns in virulence. At this stage, data can probably best contribute to how future models should be constructed. Future studies should consider (1) norms of reaction in Type 1 and Type 2 virulence, (2) spatial heterogeneity in horizontal infection, (3) co-evolution of hosts and symbionts, (4) other forms of associations (e.g., pollination, ectoparasitism), and (5) migration, mutation and local extinction over spatial templates.

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