Parasite local adaptation: Red Queen versus Suicide King

Mark F. Dybdahl and Andrew Storfer

School of Biological Sciences, PO Box 644236, Washington State University, Pullman, WA 99164-4236, USA

Parasites are generally expected to be locally adapted to their hosts, but the basis of this prediction involves two distinct areas of research: coevolutionary studies of infectivity and epidemiological studies of optimal virulence. The distinction between infectivity and virulence is sometimes blurred but is crucial to our understanding of parasite local adaptation. Recent theoretical and empirical work has greatly improved our understanding of the evolutionary processes affecting local infectivity adaptation. However, in spite of the attention paid to the evolution of virulence, only a few recent models have explicitly studied spatial variation in optimal virulence. Our understanding of parasite local adaptation will continue to improve through studies of the genetic basis of infectivity, research on spatial variation in optimal virulence in multiple-deme systems, and the combination of these two interacting components of parasite infection in theoretical and empirical studies.

Understanding evolution in host–parasite interactions in spatially structured populations is important in both basic and applied biology. Spatial variation in the interactions between parasites and their hosts is thought to be a major force in the coevolutionary process [1] and in generating biological diversity [2]. Parasite adaptation to sympatric hosts is fundamental to a prominent hypothesis for the prevalence of sexual reproduction (i.e. the Red Queen; reviewed in [3]). In addition, parasite local adaptation is important to both medicine and conservation, because, if spatial variation among host populations selects for different mechanisms of pathogen attack, treatments designed to block one strain of pathogen might be ineffective in treating others. In addition, parasites transported by anthropogenic forces beyond their historical range could result in the emergence of damaging diseases (e.g. rinderpest, brucellosis [4] and chronic wasting disease [5]). Geographical variation in host–parasite interactions is also important in biological control of pests with parasites [6] and in the success of invasive species [7].

Spatially variable host–parasite interactions are expected to generate variation in parasite performance among different host populations. Common wisdom holds that parasites should evolve faster than their hosts owing to their larger population sizes, shorter generation times and higher mutation rates. This greater evolutionary potential of parasites led to the general prediction that they should be locally adapted to their hosts, and that their fitness should decrease with distance of the host population from the source of the parasite [8,9]. Many studies of parasite local adaptation measure parasite fitness as infectivity (infection success), but parasite performance can also be measured as virulence (host damage), two distinct aspects of the infection processes. Our understanding of local parasite adaptation for these two performance measures is based on separate areas of research. For infectivity, specific predictions of parasite local adaptation have been derived from simulation models of single and multiple demes. These models show cyclical Red Queen evolutionary dynamics, where the parasite genes that result in infectivity track host defense gene frequencies, leading to high fitness in sympatric hosts. Optimal virulence has been thoroughly studied in single-deme models, but predictions about spatial variation in optimal virulence are vague. Optimal virulence should result in high parasite fitness in the sympatric host, but parasite virulence might be maladapted in other host demes, potentially driving themselves or their hosts extinct (‘Suicide King’). In general, little is known about virulence evolution in multiple demes, thus limiting our understanding of local virulence adaptation.

Here, we highlight the importance of distinguishing between infectivity and virulence when considering the evolution of parasite local adaptation, and review some recent advances in our understanding of their evolutionary dynamics in spatially structured hosts. Although we emphasize these distinctions, we also suggest that the development of theory and empirical work that couples the dynamics of virulence and infectivity is needed because of their interdependence.

Infectivity and virulence in local parasite adaptation

The distinction between infectivity and virulence is important to predictions about parasite local adaptation, especially because there is overlap in the use of these terms.

Infectivity is the ability of parasites to infect hosts (sometimes called compatibility) and is based on parasite strategies to overcome detection or reconnaissance by the host. It is measured as the prevalence of infection of a population or set of individuals, assuming that this is not biased owing to parasite-induced mortality. We use the definition of virulence commonly employed by ecologists and epidemiologists, which is the degree of host damage

Corresponding author: Mark F. Dybdahl (dybdahl@wsu.edu).

http://tree.trends.com 0169-5347/$ - see front matter doi:10.1016/S0169-5347(03)00223-4

Box 1. Genetic systems describing infectivity

Interaction loci

Interaction loci are specific genetic loci that mediate the interaction between the host and its parasite and control infectivity. For the parasite, these loci encode traits that are recognized by specific host molecular receptors. For the host, interaction loci encode the molecular receptors that control reconnaissance or detection of parasites.

Gene-for-gene

Gene-for-gene is the genetic system of interaction, typically postulated for plant–pathogen populations (although this generality has been criticized [56]) where a pathogen elicitor allele triggers a specific host response allele, leading to a defense reaction in the host. This includes recessive and universally infective alleles (sometimes called 'virulence' alleles) in the pathogen, and dominant and universally resistant alleles in the host [57]. Thus, there is cross-infectivity, where one pathogen genotype can infect multiple host genotypes. In models of the dynamics of these alleles, a cost is often assumed to exist for having universally infective parasite alleles and universally resistant host alleles to maintain allelic variation (but see [58]).

Matching alleles

Although originally called inverse matching alleles ([59], see below), most recent papers use matching alleles to describe a system where a parasite infects a host if the alleles of the parasite match those of the host at their interaction loci (reviewed in [60]; e.g. [18,61]). This model mimics host defense through a nonself recognition system, where a host recognizes parasite genotypes that do not match host genotypes. In haploid models, there is no cross-infectivity (each parasite genotype can infect only a single host genotype), but high cross-protection (each host genotype resists multiple parasite genotypes). Levels of cross-protection can vary in specific renditions of these models.

Inverse matching alleles

A parasite infects a host if the interaction alleles of the parasite do not match those of the host. This more closely mimics a specific recognition system for the host, where a host recognizes and defends against a specific set of parasite genotypes. Cross-infectivity results from multiple parasite genotypes that are unrecognized by each host genotype, but there is no cross-protection (each host genotype resists few parasite genotypes). Some papers, following [59], call this system matching alleles (see above) [62]. Matching and inverse matching allele models with a single diallelic locus are identical.

Box 2. Conditions for cyclical polymorphisms that generate spatial variation in host genetic structure

Until recently, cyclical oscillations had been well studied only for matching allele and inverse matching allele genetic systems (Box 1). These models exhibit strong cycles under a wide range of conditions, with greater amplitude and frequency under high levels of virulence [18]. It was thought that gene-for-gene models did not produce cycles, but recent models show that a variety of genetic interaction systems are likely to cycle, including those based on the modification of matching alleles [18,63], and additive polygenic characters [64,65]. Simple gene-for-gene systems produce cyclical oscillations only if there are costs to universally infective alleles [60,66].

Comparisons of different genetic systems show that they strongly determine important details of gene frequency dynamics [60,65]. For example, in a unique attempt to build a continuum between matching allele and gene-for gene models, very small departures from strict gene-for-gene models lead to cycles [60]. In addition, oscillations occurred with genetic systems intermediate between gene-for-gene and matching allele systems, even when there was no cost of universally infective alleles. However, cycles in gene-for-gene models have longer period than in matching allele models.

These predictions are based on the assumption that genetic variation for host–parasite interactions is a significant cause of variation in infection, and that environmental conditions do not overwhelm genetic variation. Consistent with this assumption, there seems to be a tight correspondence between infection rates for specific host genotypes in natural populations and in laboratory infection experiments [25,67,68]. However, little is known for any empirical animal system about the precise conformance of infectivity to the genetic systems used in models. It might be that invertebrate immune systems rely on nonself recognition mechanisms [69] as described by matching allele models, whereas vertebrate systems also have a specific recognition system depicted by inverse matching allele or gene-for-gene models [56]. One test of gene-for-gene models is to look for evidence of universally resistant host genotypes and universally virulent parasite genotypes. For animal systems, one study in *Daphnia* and a bacterial parasite did not find any evidence for these universally superior genotypes [70].

resulting from infection in terms of morbidity (pathogenicity) and mortality (lethality). Infectivity and virulence are often used interchangeably, and their entanglement comes from the multiple meanings of virulence [10]. For example, in plant pathology, virulence is synonymous with infectivity (sometimes called matching virulence), in accordance with classic gene-for-gene interactions (Box 1), whereby specific pathogen gene products trigger resistance reactions in the plant.

Infectivity and virulence are based on different mechanisms and genetic systems [11–13]. Infectivity is governed by alleles at interaction loci (Box 1) that determine the success of a parasite in a host, but virulence can be governed by a range of traits. Furthermore, having variants in the genetic recognition systems underlying mechanisms of infectivity probably entails no fitness costs, but virulence is assumed to carry a fitness cost [12].

Theoretical and empirical studies of the evolution of infectivity and virulence have been investigated separately. Simulation models of the evolution of infectivity (Box 2) consider the joint dynamics of host and parasite genetic polymorphisms, reveal cyclical oscillations in alleles at interaction loci and typically disregard population dynamics. Many multiple-deme models examine the dynamics of local adaptation for infectivity. Systems for empirical studies of infectivity evolution include both systemic and ectoparasites, ranging from parasitic plants to viruses to arthropods.

At the other end of the spectrum, empirical systems for virulence research typically involve microparasites, such as viruses, bacteria and protozoans, where the generation time differences between parasite and host are large. Consequently, theoretical models of the evolution of virulence emphasize epidemiology and parasite evolution [10,14]. Host evolution, coevolution and genetic polymorphisms related to infectivity have only recently been considered. Furthermore, only now are new models of spatial variation in optimal levels of virulence available.

Different definitions of adaptation [14] to local hosts are often used for infectivity versus virulence. For infectivity, parasite fitness can be measured as the number of infected hosts. Local adaptation is typically assessed by the analysis of infection rates in experiments involving sympatric and allopatric combinations of host and parasites (i.e. those from the same versus geographically

distinct locations). Infection experiments can be reciprocal (each host population is exposed to each parasite population), or can use sympatric and allopatric parasites on a single host, or a single parasite on sympatric and allopatric hosts (see Fig. 1 in [15]). Parasites are locally adapted if prevalence is higher in sympatric than in allopatric hosts. However, these latter two experimental designs can be misleading if parasites (or hosts) differ in overall infectivity (or resistance) [16].

For virulence, local adaptation is typically assessed by conformance to a predicted optimum. This is more difficult to define, because optimal virulence depends on a range of conditions (Box 3). When parasites are selected to become more virulent in the local host, then parasites are locally adapted if virulence is higher in sympatric than in allopatric hosts. However, the opposite holds if parasites are selected to become less virulent in local hosts. One way to circumvent this problem is to measure the virulence–fitness relationship in local adaptation studies. For example, Ebert [8] found a positive correlation between fitness measured as transmission rates and virulence-causing sporeloads produced by a pathogen in *Daphnia*, confirming that levels of virulence were adaptive.

In spite of these differences, prerequisites for local adaptation of virulence and infectivity are similar. In general, local parasite adaptation requires spatial variation in host populations (created by genetic variation or environmental variation that alters host condition), or spatial variation in ecological conditions [17], thereby generating variation in the environment that parasites encounter. In addition, parasite performance in one host population must be associated with a decrease in performance in phenotypically different host populations (i.e. a negative correlation or tradeoff between fitness in sympatric and allopatric hosts). The consequences of spatial variation in conditions that foster local adaptation are well known for infectivity, but not for virulence.

Box 3. Factors affecting optimal parasite virulence

Virulence is typically assumed to be a necessary byproduct of within-host growth and the consequent utilization of resources. Optimal levels of virulence strike a balance between parasite growth and reproduction within the host versus host survival, resulting in a tradeoff between virulence and transmission. A wide range of conditions alters this balance, and recent theoretical work has resulted in predictions as to why virulence varies within host populations [43]. Virulence is predicted to increase in homogeneous host populations [54,71] in cases of multiple infections owing to competition (i.e. 'superinfections') ([72], but see [73]), in cases of high or increased host specificity [49] and in cases of quantitative resistance to parasite damage [65]. Conversely, reduced virulence is expected to evolve in heterogeneous host populations ([65], but see [74]), in cases of reduced host specificity, in cases of qualitative resistance (i.e. resistance to infection) [65] and in cases of highly restricted parasite movement [53].

Life-history variation, such as the delay between transmission and virulence in a parasite, can affect optimal virulence; the longer the delay, the higher the expected virulence [75]. When host reproduction occurs on a larger spatial scale than does parasite infection (e.g. windborne seeds), higher virulence is expected to evolve [76].

The optimal level of virulence might be difficult to predict if the assumed positive correlation between virulence and transmission is decoupled; for example, when disease symptoms and reduced host fitness result from the host immune response, rather than from pathogen multiplication [48,73,77]. Even when a host clears an infection, host resources are used in the immunological response, rather than in reproduction or growth [48]. Recent empirical work showed no relationship between virulence and replication or reproductive fitness in a plant host–fungal parasite system [51]. A recent review also emphasizes the decoupling of, or weak correlation between virulence and transmission and the effect that this has on the dynamics of virulence evolution [78].

In reality, when both host and parasite are considered together, optimal virulence is likely in a state of flux because coevolution is a dynamic process. Because host genotype frequencies might be changing as a result of selection imposed by the parasite (and other biotic and abiotic factors), there might be a time lag as the parasite evolves toward the optimal virulence. Cycling might occur, as predicted by infectivity models; if so, determining whether a parasite is locally adapted might depend on the ecological 'snapshot' under investigation.

Infectivity

Cyclical coevolution and local infectivity adaptation

The dynamics of coevolution within populations should lead to the opportunity for local infectivity adaptation by parasites as long as host interaction allele frequencies differ among populations. This condition probably arises from a general feature of the coevolutionary process, as illustrated by simulation models of parasite infectivity: the cyclical oscillation of allele frequencies caused by time-lagged frequency-dependent selection (Red Queen dynamics). Host interaction alleles that become common drive selection on corresponding parasite alleles, and they increase in frequency. This, in turn, drives the corresponding host alleles to low frequency (assuming sufficiently strong fitness effects of the parasite) in a continual coevolutionary cycle. The resulting cyclical oscillations are likely to generate spatial variation in frequencies of interaction alleles, because cycles can be somewhat independent among populations, even when similar dynamics occur in each population. As a consequence, alleles that are common in one population are rare in others (cycles are 'out of phase'). Cycling now is known to occur under most genetic systems (Box 2). Thus, cycling potentially generates spatial variation in gene frequencies, leading to a geographical mosaic of selection faced by the parasite [18,19], and it is the conditions that govern coevolutionary cycles and their independence among populations that determine the opportunity for local infectivity adaptation.

Multiple-deme models of local infectivity adaptation

The general prediction that parasites should be more infective in sympatric hosts than in allopatric hosts has been studied explicitly with simulation models of multiple populations connected by migration. Early models showed that local parasite adaptation is more likely when migration rates are higher for parasites than for their hosts [20,21]. This seems counterintuitive because gene flow can swamp local adaptation [22]. However, under cyclical coevolution, factors that increase the evolutionary potential of the parasite increase its ability to track local host allele frequencies. In fact, the species with higher gene flow will be locally adapted [19], introducing an exception to the general expectation of parasite local

adaptation: when hosts migrate more than their parasites, they will be locally adapted to their parasite. Hence, in this scenario, hosts will be more likely to be infected by allopatric parasites than by sympatric parasites.

Recent models have further examined the factors affecting the evolutionary processes acting on local parasite adaptation. Although gene flow is conducive to local adaptation, cycles in different populations become synchronized and erase the opportunity for local parasite adaptation if gene flow becomes too high [18]. Faster parasite generation time plays only a minor role in enhancing their adaptation to local hosts, contrary to common wisdom, but it does reduce the oscillation period [18]. Enhancement in local adaptation occurs when parasites have substantially more generations per host generation, and only when there is sufficient evolutionary potential generated by mutation or migration [23]. Many of these simulation results now have been confirmed in an analytical model [19]. It is worth noting that there is no support in this body of theory for the prediction that parasite infectivity adaptation is related to geographical distance between parasite and host.

Local adaptation, in general, requires a negative correlation in infectivity between two populations, such that adaptation to one population decreases adaptation to others. Differences in gene frequencies at the interaction loci between populations should result in this pattern, especially under matching allele systems (Box 1), where parasites evolve to match local hosts. Reciprocal local adaptation, shown in cross-infection experiments, indicates this negative correlation among populations and even among specific genotypes [24–26].

Nearly all of these models use matching allele [18,27] and inverse matching allele (Box 1) genetic systems [20,21,23], which could be a problem because the details of dynamic coevolution depend on the choice of genetic system (Box 2). There are few multiple-deme gene-for-gene models (Box 1) of the coevolutionary dynamics of local adaptation, in spite of the widespread interest in the gene-for-gene model of plant–pathogen interactions. In one model that examines local adaptation using gene-for-gene interactions, local adaptation is quickly eroded under minimal levels of gene flow [18]. Most gene-for-gene models address the maintenance of variation, and some show that infectivity alleles can be maintained without assuming a cost [28,29]. Frequencies of infectivity alleles are thought to be governed by metapopulation dynamics (drift, migration or founder effects) [28], and high parasite fitness on sympatric hosts usually arises as a result of these random evolutionary processes [30]. However, more theoretical work is needed to determine the random and deterministic forces that produce patterns of pathogen adaptation in gene-for-gene systems.

Local infectivity maladaptation

Even when relative parasite migration rates and generation times favor parasite local adaptation, parasites can temporarily have higher fitness in allopatric than in sympatric hosts, referred to as parasite maladaptation. This occurs because, in systems with temporal allele frequency dynamics, the time-lagged parasite response means that the most common host genotype might be infected at low rates for part of the cycle [31]. If different populations cycle asynchronously, parasites can infect a higher proportion of host genotypes from another population [27,32]. However, predictions of maladaptation assume that identical alleles at a few loci undergo similar dynamics in all populations. If different host populations have separate sets of cycling interaction alleles, versus the same set of alleles that vary temporally in frequency, compatibility between parasites and allopatric hosts – hence maladaptation – would be impossible [32].

There are several meanings of the notion of parasite local maladaptation. In one sense, species undergoing selection in a rapidly changing environment (e.g. Red Queen cycling) are always maladapted to the sympatric host by at least one generation, and are not on an adaptive peak [14]. In addition, higher parasite fitness in allopatric hosts can imply greater adaptation to that host, but this does not represent a response to a previous history of selection when maladaptation results from out-of-phase cycling among populations.

Some studies support the prediction that parasites can be maladapted ([33–36], reviewed in [15]). However, many studies have shown parasite local adaptation for infectivity with cross-infection experiments, and the predictions regarding gene flow in multiple deme models hold in the few studies that have estimated both local adaptation and migration rates [8,34,37–39]. Local adaptation at regional scales has also been well described for a plant–pathogen system, in spite of overall differences among regions in infectivity and resistance [16,40].

There are several alternative explanations for patterns of adaptation and maladaptation other than out-of-phase cycling. First, comparisons of local parasite adaptation across different studies and systems are hampered by lack of a common currency for intensity of selection and differential adaptation. Local adaptation might be less likely in some systems, especially those involving parasites or pathogens that have minor effects on host population regulation (M.E. Hochberg, pers. commun.) or individual fitness [18]. Second, a rare parasite genotype in one population might be infective on one or more common host genotypes in a second population. An infection experiment that raises rare parasite genotypes to a high dose could produce a pattern that is consistent with maladaptation. Third, local adaptation could be undetected under diffuse coevolution (where parasites with a broad host range interact with numerous hosts) if the host under study is not being tracked by the parasite [15]. Finally, local maladaptation can also arise when species interactions occur in coevolutionary hot spots and cold spots, locations where interacting species have strong reciprocal effects on each other's fitness versus one-sided effects. Maladaptation occurs when populations in cold spots are pulled from their adaptive peaks by migration from hot spots; in fact, the degree of maladaptation can cycle over time [41,42].

Virulence

Although there has been extensive interest in virulence evolution (reviewed in [43]), there is little theoretical work

upon which to base predictions about spatial variation among host populations in virulence adaptation. Most theoretical research on optimal virulence has focused on single deme models of the parasite, with little treatment of geographical variation in virulence among host populations [13,44]. In addition, most empirical virulence studies have been done with laboratory populations.

Past research on conditions that alter optimal virulence within demes, such as variation in life-history traits, host density, or superinfections (Box 3), can serve as a starting point for predictions about local virulence adaptation. Spatial variation in these conditions among host populations provides the opportunity for local selection, which results in spatial variation in optimal virulence levels. Also important for local virulence adaptation is a tradeoff in performance among different host populations. Serial passage experiments (i.e. consecutive infection of several host individuals, usually from inbred lines or clones, or continuous passage through cell-culture lines) clearly show that the increasing adaptation of a parasite population to a host strain usually results in increased virulence, accompanied by attenuation of virulence on previous hosts [9]. Finally, recent models explicitly address spatial variation in optimal virulence.

Spatial variation in optimal virulence

Variation in optimal virulence might be inevitable, because spatial variation in conditions that alter optimal virulence is common. The causes include: (1) variation in host genotypes among demes; (2) differences in environmental quality; (3) ecological differences; or (4) the strength of reciprocal selection between host and parasite [13].

Hosts and parasites exhibit spatial variation in population genetic structure [13,17]. Genetic differences among host demes can result in variation in mechanisms by which hosts defend against parasite damage, thereby driving spatial variation in strategies used by parasites to evade host immunity. Genetic variation can result in differences in the timing of life-history events or background mortality among host populations, both of which can influence parasite virulence levels (Box 3). For example, in a recent model with rarely considered coevolutionary feedback between host and pathogen, high host mortality favors reduced parasite virulence and late host reproduction when environmental conditions enable rapid host growth [45].

In most virulence models, however, host populations and their environments are assumed to be constant (see [46]). Of course, environments are generally patchy and variable in quality, and this can also explain geographical differences in optimal virulence. In one theoretical study, decreasing habitat quality led to low virulence, where the outcome depends on how the parasite affects density-dependent competition among hosts [47]. However, in a model that considers virulence as a result of either parasite exploitation or costs of host immunological up-regulation (Box 3, [48]), poor habitat quality leads to high virulence. If the host experiences high background mortality in a poor quality habitat, the model predicts the coevolution of high immunological expenditure by the host and high rate of exploitation by the parasite (and the converse in habitats with low background mortality). Although not explicitly examined by this model, one might expect that parasites would have optimal levels of virulence in sympatric hosts as a result of spatial variation in host background mortality.

Ecological factors, such as source–sink dynamics, can affect local adaptation [13]. Increased parasite immigration from a source might indirectly limit local adaptation in a sink, when the hosts in the sink are coevolving with their parasites. In this case, parasite immigration further reduces the number of susceptible hosts, effectively lowering the fitness of more virulent parasites. The nature of interactions between hosts and parasites can also be affected by whether they occur at geographical boundaries or in the center of their ranges, or by variation in the community in which both species interact (e.g. the presence of alternative hosts or enemies) [17].

In the geographical mosaic theory of coevolution, the strength of coevolutionary interactions varies spatially in hot spots and cold spots [1]. Increased pathogen specificity, which is likely to occur in a hot spot relative to a cold spot, is expected to result in increased pathogen virulence [49]. Conversely, cold spots probably favor decreased pathogen specificity, resulting in decreased virulence.

Empirical studies of virulence variation

The prediction that parasites should be more virulent in sympatric hosts as opposed to allopatric hosts receives support from serial passage experiments showing that long-term selection increases virulence [9]. However, given the range of predictions for optimal virulence (Box 3), failure to detect higher virulence in a sympatric compared with an allopatric host population does not necessarily mean that a parasite is 'maladapted'. Low virulence might be optimal for a particular parasite–host combination, resulting in higher virulence in allopatric hosts.

Several empirical studies support the prediction of a negative correlation between distance from host source and parasite virulence, but there are exceptions. In a study of monarch butterflies and a protozoan parasite, the virulence of one parasite strain was higher than another, regardless of whether local or allopatric hosts were infected [50]. Also, in a plant–fungal pathogen system, although fungal strains caused slightly higher damage and had slightly higher fitness in sympatric versus allopatric hosts, these trends were not significant [51].

Local adaptation for virulence might depend on the spatial scale of the study. For example, a study of bumblebees and a protozoan parasite showed that, contrary to expectations, allopatric protozoans had higher virulence (mortality) than did local ones in a long-distance transplant experiment (i.e. were locally maladapted). However, over a smaller spatial scale, the prediction of local adaptation was met, with local parasites causing more damage to host fitness than did allopatric parasites [33].

Environmental variation can also affect whether parasites appear locally adapted. A study of seabirds and tick parasites [52] showed that, in a year when resources were abundant, local ticks were more virulent (i.e. there was a larger number of ticks per host) in local hosts than in allopatric hosts. However, when environmental quality was poor, a relationship between geographical distance

Box 4. Future directions

Infectivity

- There remain empirical and theoretical opportunities for a better understanding of local infectivity adaptation. Simulation models are sensitive to genetic interaction systems, and empirical data about the conformance of natural systems with specific genetic systems are needed. Models of gene-for-gene systems (Box 1), especially those involving multiple populations, are also relatively unexplored. Coevolution models are predominantly haploid, and so models that explore diverse ploidy are needed, although the dynamics in such models are more complex [79].
- Multiple-deme models with simple genetic systems suggest that maladaptation might be common. They show that a host can be weakly infected by its sympatric parasite, but strongly infected by an allopatric parasite, given the limited number of genotypes of simple model systems. This might not be true under genetic systems with more complex genetic structure. Studies are needed to determine whether resistance genotypes are shared, as assumed by models, or are distinct among populations. In addition, replicate studies of local adaptation using the same system, and at different spatial scales, are needed to see whether cycles lead to temporary maladaptation.

Virulence

- There are very few multiple-deme models of optimal virulence. Predictions of local virulence adaptation require models, analogous with those for infectivity, that combine local dynamics with gene flow among demes.
- Parasite adaptation for virulence does not necessarily mean host maladaptation, as it can for infectivity. Parasite virulence can lead to highest fitness on its sympatric host, but this does not necessarily mean that this host will not experience higher virulence from an allopatric parasite. Empirical studies should examine single host strains with a range of parasite strains to investigate which parasite strain has the highest fitness.
- There is the potential for evolution of polyphenism (plasticity) for virulence [80]. If so, studies of local virulence adaptation should consider optimal levels of plasticity or induced defense, which can vary among host populations.

Infectivity and virulence

- Infectivity and virulence are distinct steps in the infection process, but they do interact [47]. Parasite infectivity determines the number of susceptible hosts, which, in turn, affects optimal virulence. Virulence levels strongly influence the dynamics of infectivity alleles. Studies will be more realistic if they examine their joint evolutionary dynamics. For example, one new model [49] shows that increased parasite specificity for infection results in increased virulence. In a plant–pathogen system, a tradeoff between infectivity and virulence might explain the maintenance of variation, given the presence of highly infective pathogen genotypes [40].
- The infectivity and virulence of novel parasites remains poorly understood. Predictions about the relationship between phylogenetic distance and virulence, which rely on observational data, should be further tested empirically with infection experiments using novel hosts [55].

and virulence was not observed in the parasite, suggesting that all hosts were equally susceptible.

Because virulence varies with environmental quality, as environments degrade owing to anthropogenic activities over short timescales, parasites might be maladapted for virulence, driving their hosts and/or themselves locally extinct. Recent work suggests that extinction can occur with a high degree of host spatial structuring, where local transmission can remain high in spite of low global host density [53]; such spatial structuring can occur as a result of anthropogenic habitat fragmentation.

Further study of spatial variation in optimal virulence will be valuable for several reasons. At present, it is difficult to predict the level of virulence for a parasite introduced to a distant, novel host population. This is troublesome because novel parasitism has increased as humans move parasites away from their historical geographical ranges. In theory, virulence of new parasites should decrease with phylogenetic distance between the new and native host, yet many novel parasites have high virulence (e.g. *Ebola* in humans, or Dutch elm disease) [54]. However, these cases might represent a biased sample because low virulence novel encounters remain undetected [54]. The frequency of such encounters is unknown, so it is also possible that novel encounters are rarely infective, as predicted by the models discussed above, but are highly virulent. The value of theory will be limited to providing clues to these questions [10], and empirical work is also very limited. One study suggests that phylogenetic relationship is associated with neither the likelihood of novel infections, nor levels of virulence, but is associated with levels of infectivity [55].

Conclusions

The process of parasite adaptation to local hosts, and the consequences for parasite performance on allopatric or novel hosts, will be important in both basic and applied biology. Recent studies of two distinct aspects of parasite evolution, infectivity and virulence, have clarified the conditions for local adaptation. Nevertheless, further work will be helpful, especially on the joint effects of infectivity and virulence (Box 4). Empirical studies are needed to verify genetic models of local infectivity adaptation. Optimal virulence theory in single populations provides a starting point for predictions about local virulence adaptation, and further investigation of spatial variation in optimal virulence using multiple populations is necessary for predicting, for example, the effect of parasites that move outside their historical range. Finally, studying interactions between infectivity and virulence, and their joint evolutionary dynamics, will be a valuable step in building an integrated view of parasite local adaptation.

Acknowledgements

We thank Ben Bolker, Jesse Brunner, Jim Collins, Stephanie Kane, Curt Lively, Steve Mech and Leslie Riley for discussions. Comments from Michael Hochberg, Yannis Michalakis and an anonymous reviewer also provided valuable contributions. This work was supported by NSF DEB 9907373 (M.F.D.) and NSF IBN 9977063 (A.S.).

References

1 Thompson, J.N. (1994) *The Coevolutionary Process*, University of Chicago Press
2 Thompson, J.N. (1999) The evolution of species interactions. *Science* 284, 2116–2118
3 Lively, C.M. (1996) Host–parasite coevolution and sex – do interactions between biological enemies maintain genetic variation and cross-fertilization? *Bioscience* 46, 107–114
4 Daszak, P. *et al.* (2000) Emerging infectious diseases of wildlife: threats to biodiversity and human health. *Science* 287, 443–449

5 Yam, P. (2003) Shoot this deer. *Sci. Am.* 288, 39–43
6 Lafferty, K.D. and Kuris, A.M. (1996) Biological control of marine pests. *Ecology* 77, 1989–2000
7 Torchin, M.E. *et al.* (2003) Introduced species and their missing parasites. *Nature* 421, 628–630
8 Ebert, D. (1994) Virulence and local adaptations of a horizontally transmitted parasite. *Science* 265, 1084–1086
9 Ebert, D. (1998) Experimental evolution of parasites. *Science* 282, 1432–1435
10 Bull, J. (1994) Virulence. *Evolution* 48, 1423–1437
11 Frank, S.A. (2000) Specific and non-specific defense against parasitic attack. *J. Theor. Biol.* 202, 283–304
12 Rigby, M.C. *et al.* (2002) Why should parasite resistance be costly? *Trends Parasitol.* 18, 116–120
13 Hochberg, M.E. and Holt, R.D. (2002) Biogeographical perspectives on arms races. In *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management* (Dieckmann, U., ed.), pp. 197–209, Cambridge University Press
14 Crespi, B.J. (2000) The evolution of maladaptation. *Heredity* 84, 623–629
15 Lajeunesse, M.J. and Forbes, M.R. (2002) Host range and local parasite adaptation. *Proc. R. Soc. Lond. Ser. B* 269, 703–710
16 Thrall, P.H. *et al.* (2002) Local adaptation in the *Linum marginale–Melampsora lini* host–pathogen interaction. *Evolution* 56, 1340–1351
17 Holt, R.D. and Hochberg, M.E. (2002) Virulence on the edge: a source–sink perspective. In *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management* (Dieckmann, U., ed.), pp. 104–119, Cambridge University Press
18 Lively, C.M. (1999) Migration, virulence, and the geographic mosaic of adaptation by parasites. *Am. Nat.* 153, S34–S47
19 Gandon, S. (2002) Local adaptation and the geometry of host–parasite coevolution. *Ecol. Lett.* 5, 246–256
20 Gandon, S. *et al.* (1996) Local adaptation and gene-for-gene coevolution in a metapopulation model. *Proc. R. Soc. Lond. Ser. B* 263, 1003–1009
21 Gandon, S. *et al.* (1998) Differential adaptation in spatially heterogeneous environments and host–parasite coevolution. In *Genetic Structure and Local Adaptation in Natural Insect Populations* (Mopper, S. and Strauss, S., eds), pp. 325–340, Chapman & Hall
22 Slatkin, M. (1987) Gene flow and the geographic structure of natural populations. *Science* 236, 787–792
23 Gandon, S. and Michalakis, Y. (2002) Local adaptation, evolutionary potential and host–parasite coevolution: interactions between migration, mutation, population size and generation time. *J. Evol. Biol.* 15, 451–462
24 Lively, C.M. (1989) Adaptation by a parasitic trematode to local populations of its snail host. *Evolution* 43, 1663–1671
25 Dybdahl, M.F. and Lively, C.M. (1998) Host–parasite coevolution: evidence for rare advantage and time-lagged selection in a natural population. *Evolution* 52, 1057–1066
26 Lively, C.M. and Dybdahl, M.F. (2000) Parasite adaptation to locally common host genotypes. *Nature* 405, 679–681
27 Morand, S. *et al.* (1996) Parasite–host coevolution and geographic patterns of parasite infectivity and host susceptibility. *Proc. R. Soc. Lond. Ser. B* 263, 119–128
28 Damgaard, C. (1999) Coevolution of a plant host–pathogen gene-for-gene system in a metapopulation model without cost of resistance or cost of virulence. *J. Theor. Biol.* 201, 1–12
29 Thrall, P.H. and Burdon, J.J. (2000) Effects of resistance variation in a natural plant host–pathogen metapopulation on disease dynamics. *Plant Pathol.* 49, 1–8
30 Burdon, J.J. and Thompson, J.N. (1995) Changed patterns of resistance in a population of *Linum marginale* attacked by the rust pathogen *Melampsora lini*. *J. Ecol.* 83, 199–206
31 Dybdahl, M.F. and Lively, C.M. (1995) Host–parasite interactions: infection of common clones in natural populations of a freshwater snail (*Potamopyrgus antipodarum*). *Proc. R. Soc. Lond. Ser. B* 260, 99–103
32 Kaltz, O. and Shykoff, J. (1998) Local adaptation in host–parasite systems. *Heredity* 81, 361–370
33 Imhoof, B. and Schmid-Hempel, P. (1998) Patterns of local adaptation of a protozoan parasite to its bumblebee host. *Oikos* 82, 59–65
34 Kaltz, O. *et al.* (1999) Local maladaptation in the anther-smut fungus *Microbotryum violaceum* to its host plant *Silene latifolia*: evidence from a cross-inoculation experiment. *Evolution* 53, 395–407
35 Oppliger, A. *et al.* (1999) Parasite local maladaptation in the Canarian lizard *Gallotia galloti* (Reptilia: Lacertidae) parasitized by haemogregarian blood parasite. *J. Evol. Biol.* 12, 951–955
36 Koskela, T. *et al.* (2000) Local adaptation of a holoparasitic plant, *Cuscuta europaea*: variation among populations. *J. Evol. Biol.* 13, 749–755
37 Dybdahl, M.F. and Lively, C.M. (1996) The geography of coevolution: comparative population structures for a snail and its trematode parasite. *Evolution* 50, 2264–2275
38 Davies, C.M. *et al.* (1999) Host–parasite population genetics: a cross-sectional comparison of *Bulinus globosus* and *Schistosoma haematobium*. *Parasitology* 119, 295–302
39 Delmotte, F. *et al.* (1999) Host and parasite population structure in a natural plant–pathogen system. *Heredity* 82, 300–308
40 Thrall, P.H. and Burdon, J.J. (2003) Evolution of virulence in a plant host–pathogen metapopulation. *Science* 299, 1735–1737
41 Gomulkiewicz, R. *et al.* (2000) Hot spots, cold spots, and the geographic mosaic theory of coevolution. *Am. Nat.* 156, 156–174
42 Thompson, J.N. *et al.* (2002) Coevolution and maladaptation. *Integr. Comp. Biol.* 42, 381–387
43 Galvani, A.P. (2003) Epidemiology meets evolutionary ecology. *Trends Ecol. Evol.* 18, 132–139
44 Lipsitch, M. and Nowak, M.A. (1995) The evolution of virulence in sexually transmitted HIV/AIDS. *J. Theor. Biol.* 174, 427–440
45 Koella, J.C. and Restif, O. (2001) Coevolution of parasite virulence and host life history. *Ecol. Lett.* 4, 2017–2214
46 Koella, J.C. (2000) Coevolution of parasite life cycles and host life-histories. In *Evolutionary Biology of Host–Parasite Relationships: Theory Meets Reality* (Dieckmann, U., ed.), pp. 120–185, Elsevier Science
47 Hochberg, M.E. and van Baalen, M. (2000) A geographic perspective of virulence. In *Evolutionary Biology of Host–Parasite Relationships: Theory Meets Reality* (Dieckmann, U., ed.), pp. 81–96, Elsevier Science
48 Day, T. and Burns, J.G. (2003) A consideration of patterns of virulence arising from host–parasite coevolution. *Evolution* 57, 671–676
49 Kirchner, J.W. and Roy, B.A. (2002) Evolutionary implications of host–pathogen specificity: fitness consequences of pathogen virulence traits. *Evol. Ecol. Res.* 4, 27–48
50 Altizer, S.M. (2001) Migratory behaviour and host–parasite coevolution in natural populations of monarch butterflies infected with a protozoan parasite. *Evol. Ecol. Res.* 3, 611–632
51 Zahn, J. *et al.* (2002) Adaptation and effect of host genotype on the rate of pathogen evolution: an experimental test in a plant pathosystem. *J. Evol. Biol.* 15, 634–647
52 McCoy, K.D. *et al.* (2002) Local adaptation of the ectoparasite *Ixodes uriae* to its seabird host. *Evol. Ecol. Res.* 4, 441–456
53 Haraguchi, Y. and Sasaki, A. (2000) The evolution of parasite virulence and transmission rate in a spatially structured population. *J. Theor. Biol.* 203, 85–96
54 Ebert, D. (1999) The evolution and expression of parasite virulence. In *Evolution in Health and Disease* (Stearns, S., ed.), pp. 161–172, Oxford University Press
55 Perlman, S.J. and Jaenike, J. (2003) Infection success in novel hosts: an experimental and phylogenetic study of *Drosophila*-parasitic nematodes. *Evolution* 57, 544–557
56 Frank, S.A. (1994) Recognition and polymorphism in host–parasite genetics. *Philos. Trans. R. Soc. Lond. Ser. B* 346, 283–293
57 Thompson, J.N. and Burdon, J.J. (1992) Gene-for-gene coevolution between plants and parasites. *Nature* 360, 121–125
58 Damgaard, C. (1999) Coevolution of a plant host–pathogen gene-for-gene system in a metapopulation model without cost of resistance or cost of virulence. *J. Theor. Biol.* 201, 1–12
59 Frank, S.A. (1992) Models of plant–pathogen coevolution. *Trends Genet.* 8, 213–219
60 Otto, S.P. and Michalakis, Y. (1998) The evolution of recombination in changing environments. *Trends Ecol. Evol.* 13, 145–151
61 Agrawal, A. and Lively, C.M. (2002) Infection genetics: gene-for-gene versus matching-allele models, and all points in between. *Evol. Ecol. Res.* 4, 1–12
62 Gandon, S. *et al.* (1996) Local adaptation and gene-for-gene coevolution in a metapopulation model. *Proc. R. Soc. Lond. Ser. B* 263, 1003–1009

63 Gandon, S. and Michalakis, Y. (2002) Local adaptation, evolutionary potential and host–parasite coevolution: interactions between migration, mutation, population size and generation time. *J. Evol. Biol.* 15, 451–462
64 Gravilets, S. (1997) Coevolutionary chase in exploiter–victim systems with polygenic characters. *J. Theor. Biol.* 186, 527–534
65 Gandon, S. and Michalakis, Y. (2000) Evolution of parasite virulence against qualitative and quantitative host resistance. *Proc. R. Soc. Lond. Ser. B* 267, 985–990
66 Sasaki, A. (2000) Host–parasite coevolution in a multilocus gene-for-gene system. *Proc. R. Soc. Lond. Ser. B* 267, 2183–2188
67 Little, T.J. and Ebert, D. (2000) The cause of parasitic infection in natural populations of *Daphnia* (Crustacea: Cladocera): the role of host genetics. *Proc. R. Soc. Lond. Ser. B* 267, 2037–2042
68 Little, T.J. and Ebert, D. (2001) Temporal patterns of genetic variation for resistance and infectivity in a *Daphnia*–microparasite system. *Evolution* 55, 1146–1152
69 Grosberg, R.K. and Hart, M.W. (2000) Mate selection and the evolution of highly polymorphic self/nonself recognition genes. *Science* 289, 2111–2114
70 Carius, H.J. *et al.* (2001) Genetic variation in a host–parasite association: potential for coevolution and frequency dependent selection. *Evolution* 55, 1136–1145
71 Regoes, R.R. *et al.* (2000) Evolution of virulence in a heterogeneous host population. *Evolution* 54, 64–71
72 Levin, B.R. and Bull, J.J. (1994) Short-sighted evolution and the virulence of pathogenic micro-organisms. *Trends Microbiol.* 2, 76–81
73 Mackinnon, M.J. and Read, A.F. (1999) Genetic relationships between parasite virulence and transmission in the rodent malaria *Plasmodium chabaudi*. *Evolution* 53, 689–703
74 Ganusov, V.V. *et al.* (2002) Within-host population dynamics and the evolution of microparasites in a heterogeneous host population. *Evolution* 56, 213–223
75 Day, T. (2003) Virulence evolution and the timing of parasite life history events. *Trends Ecol. Evol.* 18, 113–118
76 Boots, M. and Sasaki, A. (2000) The evolutionary dynamics of local infection and global reproduction in host–parasite interactions. *Ecol. Lett.* 3, 181–185
77 Lipsitch, M. and Moxon, E.R. (1997) Virulence and transmissibility of pathogens: what is the relationship? *Trends Microbiol.* 5, 31–37
78 Ebert, D. and Bull, J.J. (2003) Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends Microbiol.* 11, 15–20
79 Switzes, J.M. and Moody, M.E. (2001) Coevolutionary interactions between a haploid species and a diploid species. *J. Math. Biol.* 42, 175–194
80 Pfennig, K.S. (2001) Evolution of pathogen virulence: the role of variation in host phenotype. *Proc. R. Soc. Lond. Ser. B* 268, 755–760