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REVIEW

Variation in infectivity and aggressiveness in space and time in wild host–pathogen systems: causes and consequences

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Abstract

Variation in host resistance and in the ability of pathogens to infect and grow (i.e. pathogenicity) is important as it provides the raw material for antagonistic (co)evolution and therefore underlies risks of disease spread, disease evolution and host shifts. Moreover, the distribution of this variation in space and time may inform us about the mode of coevolutionary selection (arms race vs. fluctuating selection dynamics) and the relative roles of G × G interactions, gene flow, selection and genetic drift in shaping coevolutionary processes. Although variation in host resistance has recently been reviewed, little is known about overall patterns in the frequency and scale of variation in pathogenicity, particularly in natural systems. Using 48 studies from 30 distinct host–pathogen systems, this review demonstrates that variation in pathogenicity is ubiquitous across multiple spatial and temporal scales. Quantitative analysis of a subset of extensively studied plant–pathogen systems shows that the magnitude of within-population variation in pathogenicity is large relative to among-population variation and that the distribution of pathogenicity partly mirrors the distribution of host resistance. At least part of the variation in pathogenicity found at a given spatial scale is adaptive, as evidenced by studies that have examined local adaptation at scales ranging from single hosts through metapopulations to entire continents and – to a lesser extent – by comparisons of pathogenicity with neutral genetic variation. Together, these results support coevolutionary selection through fluctuating selection dynamics. We end by outlining several promising directions for future research.

Introduction

The maintenance of diversity in host resistance and pathogenicity (i.e. the ability to infect and grow; see section *Definitions*) of pathogens has intrigued empiricists and theoreticians for decades (Haldane, 1949; Bergelson *et al.*, 2001; Brown & Tellier, 2011). Importantly, genetic variation in patterns of host susceptibility and pathogen infectivity and aggressiveness are essential underlying factors influencing disease epidemiology (Wolfe, 1985; Garrett & Mundt, 1999; Thrall & Burdon, 2000; Mundt, 2002) and the emergence and spread of new diseases (Parker & Gilbert, 2004; Friesen *et al.*, 2006; Gomez *et al.*, 2008; Fisher *et al.*, 2012). However, we still have little empirical data on how ecological and evolutionary processes interact to influence the generation and maintenance of spatial and temporal variation in natural host–pathogen interactions.

Our current understanding of the maintenance of variation in resistance and pathogenicity is largely based on theoretical predictions. Antagonistic coevolution between hosts and pathogens has been invoked as a key driver of biological diversity, but only negative frequency-dependent selection (or fluctuating selection dynamics: FSD) can stably maintain within-population genetic diversity. Diversity results as the most common

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host genotypes are also those most susceptible to infection, as the pathogen genotypes that specialize on those host genotypes dominate. This leads to parasites driving continual selection against common genotypes, favouring rare genotypes and promoting diversity through time (Lively, 2001). Coevolutionary dynamics can be viewed as a continuum, with escalation of defence and counter-defence (directional arms race dynamics; ARD) at one extreme and selection for rare host and parasite genotypes (FSD) at the other extreme. Crucially, as a result of mutational limitations (Lenski, 1984) or costs associated with defence and counter-defence (Frank, 1994; Sasaki & Godfray, 1999; Sasaki, 2000), ARD are proposed to be short lived, with coevolution either stopping or giving way to FSD. To date, the best empirical support for ARD comes from microcosm studies of bacteria–phage coevolution (Buckling & Rainey, 2002), and the few available investigations of natural associations lend support for FSD (Decaestecker *et al.*, 2007; Gómez & Buckling, 2011; Thrall *et al.*, 2012). Although the mode of selection is the central tenet of coevolutionary research, few systems have the biological properties or the resources available to undertake studies that actually track coevolutionary dynamics through space and time (Gaba & Ebert, 2009). Hence, assessing patterns of variation in host–parasite interactions can help us understand the relative importance of different modes of selection (FSD or ARD).

Furthermore, numerical simulations show that these coevolutionary dynamics yield very different patterns of adaptation over time (Gandon *et al.*, 2008; Gandon & Day, 2009). Under the hypothesis that coevolutionary dynamics across multiple populations are not synchronized, the dynamics over space are very similar to the dynamics over time under FSD, leading to pathogen local adaptation (Gandon *et al.*, 2008). Because evolution is directional under ARD, expected patterns of adaptation are less clear as the emergence of local adaptation requires some differentiation among populations. In this case, for local adaption to occur, different populations need to reach adaptation through different routes (i.e. different genes involved in local adaptation; Gandon *et al.*, 2008). Hence, detecting local adaptation according to the metric of higher pathogen performance with foreign vs. local host genotypes (Kawecki & Ebert, 2004) may be less likely under ARD than it is under FSD.

Although FSD can maintain diversity, these predictions are complicated by variation in the assumed genetic architectures underlying these key traits. On the one hand, the majority of scientists working on plant–pathogen interactions have – stemming from the pioneering experimental work of Flor (1956) – largely focused on the maintenance of diversity when hosts and pathogens interact via major gene-for-gene mechanisms (Leonard, 1977; Bergelson *et al.*, 2001). Here, many plant pathogens (including fungi, bacteria and viruses; Thompson & Burdon, 1992), insects (Hatchett & Gallun, 1970; Bangham *et al.*, 2007) and microbial systems (Buckling & Rainey, 2002; Forde *et al.*, 2004) have been shown to conform to the gene-for-gene (GFG) model. According to GFG, each host resistance gene produces a receptor that can recognize a particular pathogen infectivity effector. A key feature of this model is that a pathogen can become 'universally infective', and a cost of infectivity is usually required to maintain variation in host resistance and pathogenicity (Bergelson *et al.*, 2001; but see e.g. Thrall & Burdon, 2002 and Damgaard, 1999). In contrast, biologists studying host–parasite interactions in animal and human populations have frequently adopted the matching-allele model (MAM), which is based on the self/nonself recognition mechanism in invertebrates (Agrawal & Lively, 2002). Notably, empirical support for the MAM is only recently emerging, possibly because studies of the genetics of the interactions are hampered by difficulties in generating genetically pure parasite isolates (Box A). In this model, resistance and infection are a result of specific matches between host and pathogen genotypes, and no 'universally infective' pathogen can emerge. Hence, there is no need to invoke costs of resistance and infectivity to maintain variation.

Despite this dichotomy in modelling approaches, theoreticians now generally agree that both theoretical frameworks can explain cyclic dynamics of allele frequencies, and thereby maintain diversity in resistance and pathogenicity (Agrawal & Lively, 2002; Dybdahl & Storfer, 2003; Laine & Tellier, 2008). The MAM is prone to produce cycles (and thereby conserve polymorphism) under a wide range of parameter values. In contrast, models of gene-for-gene systems have to invoke a certain level of natural realism – like spatial population structure – to promote the maintenance of polymorphisms (Thrall & Burdon, 2002; Laine & Tellier, 2008; Brown & Tellier, 2011). In gene-for-gene models, stabilization of polymorphisms is mainly related to factors that uncouple host and pathogen life cycles in time or space (resulting in negative direct frequency-dependent selection; Tellier & Brown, 2007), such as spatial heterogeneity in selection pressure (e.g. due to spatial variation in disease severity, or in the cost of resistance and pathogenicity; Laine & Tellier, 2008; Wolinska & King, 2009; Mostowy & Engelstädter, 2011; Tellier & Brown, 2011). Factors that promote the persistence of dynamic polymorphisms in time (rather than creating stable equilibria) are linked to genetic complexity (e.g. the number of genes involved) and, again, spatial structuring of host and pathogen populations.

In addition to local selection, there is potential for various nonselective processes to influence the distribution of variation among populations. Isolation-by-distance processes promote asynchrony among populations, and hence, localized dispersal allows the maintenance of spatial variation in genotype frequen-

Box A: Variation in infectivity and aggressiveness in animal–pathogen systems

Studies on spatial variation in infectivity and aggressiveness in animal-parasite systems are relatively infrequent as compared to plant pathogen studies (Table A). This may partly be due to the long-standing experimental work with purified pathogen genotypes in plant studies (Barrus, 1911; Flor, 1942), whereas studies on animal pathogens have often used inoculation material potentially consisting of a mixture of multiple pathogen genotypes. However, several recent advancements allow for a first comparison of plant–pathogen and animal–pathogen interactions.

For example, a recent study using single clones of the bacterial parasite *Pasteuria ramosa* in *Daphnia magna* revealed strong genotype-by-genotype interactions among host and pathogen (Luijckx *et al.*, 2011). This study then suggests that strong genotype-by-genotype interactions are a more general feature of host–pathogen interactions than previously envisioned. However, although strong genotype-by-genotype interactions may be prevalent in both animal and plant hosts, the interaction type is not necessarily the same. Although plant–pathogen interactions frequently confer to the gene-for-gene interaction, the first evidence for animal–pathogen interactions for *Pasteuria ramosa* in *Daphnia magna* indicates that a matching-allele system is more likely (Luijckx *et al.*, 2012).

Given these first characterizations of genotype-by-genotype interactions in animal pathosystems, we hope that future studies in this field will explore the spatial and temporal dimensions of variation in pathogenicity using animal pathogens. Importantly, the first evidence suggests that variation in pathogenicity in animal–pathogen systems is comparable with that of plant –pathogen systems, where variation in pathogenicity is common both within and among populations (Table A). Moreover, a study by Carius *et al.* (2001) concluded – as based on high-within population variation in pathogenicity – that within-population processes are dominant. Future studies may then provide further insights into the differences and similarities of plant and animal pathosystems.

Table A A list of studies assessing the spatial scale of variation in pathogenicity in wild animal–pathogen interactions.

Reference	Species	No. pathogen populations	Spatial scale (min. and max. distance separating pathogen populations, km)	How pathogenicity is measured	At what scale variation in pathogenicity is detected
Altizer (2001)	*Danaus plexippus* (monarch butterfly)–*Ophryocystis elektroscirrha* (neogregarine protozoan parasite)	3	*c*. 2000–3000	Inoculations	Between populations (within population not tested)
Carius *et al.* (2001)	*Daphnia magna* (planktonic crustacean)–*Pasteuria ramosa* (bacterial endoparasite)	2	Single population (for each of two populations)	Inoculations	Within population
Ebert (1994)	*Daphnia magna* (planktonic crustacean)–*Glugoides intestinalis* (microsporidium)	3	0.5–1.5	Inoculations	Between populations (within population not tested)
Ebert *et al.* (1998)	*Daphnia magna* (planktonic crustacean)–*Pasteuria ramosa* (bacterial endoparasite)	3	50–2500	Inoculations	Between populations (within population not tested)
Imhoof & Schmid-Hempel (1998)	*Bombus terrestris* (bumblebee)–*Crithidia bombi* (trypanosome intestinal parasite)	3 (local scale); 3 (regional scale)	18–37 (local scale)/*c*. 80–200 (regional scale)	Inoculations	Between populations and between regions
Oppliger *et al.* (1999)	*Gallotia galloti* (Canarian lizard)–haemogregarine genus (blood parasite)	3	20–30	Inoculations	Between populations

cies through the emergence of fixed or moving spatial patterns (Gandon, 2002; Sasaki *et al.*, 2002). A predominance of neutral variation is likely to occur when selection is weak relative to mutation, genetic drift and the homogenizing effect of gene flow (Slatkin, 1987; Hedrick, 2000). As the balance between genetic drift, mutation, selection and gene flow varies with spatial scale, the degree of pathogen adaptation may likewise vary across spatial scales. Importantly, as the majority of wild plants, animals and pathogens are patchily distributed across landscapes (Burdon, 1993; Hanski, 1999), spatial structure is likely to play a critical role in maintaining polymorphism in host resistance and pathogenicity in a natural setting (Frank, 1991; Thrall & Antonovics, 1995; Sasaki, 2000; Sasaki *et al.*, 2002; Thrall & Burdon, 2002;

Thrall *et al.*, 2002; Gavrilets & Michalakis, 2008; Laine & Tellier, 2008; Tellier & Brown, 2011). Characterization of spatial and temporal patterns in the distribution of pathogenicity and host resistance can hence be used to dissect the mode of coevolutionary selection, relative importance of gene flow, mutation and genetic drift and provide an empirical base, and future directions, for theoretical studies. Although the spatial distribution of variation in host resistance has been recently reviewed (Salvaudon *et al.*, 2008; Laine *et al.*, 2010), there has been no consolidated effort to review and quantify levels of variation in pathogenicity present in natural pathogen populations and how such variation is distributed in either space or time (but see Stukenbrock & McDonald, 2008 for several agricultural examples).

Here, we characterize patterns of variation in pathogenicity in wild host–pathogen associations across a range of spatial scales: within individual hosts, within host populations, among host populations (i.e. metapopulations) and among broader geographical regions. We also examine at what spatial scale(s) pathogenicity varies through time. More specifically: (i) Given the difficulties of maintaining polymorphism in pathogenicity in gene-for-gene models under empirically realistic parameter values (Bergelson *et al.*, 2001; Brown & Tellier, 2011), we first evaluate the frequency of pathogenic variation at multiple spatial scales across 45 published studies on wild host–pathogen interactions. Importantly, variation in pathogenicity across spatial and temporal scales in a large fraction of study systems will indicate that factors that increase the maintenance of pathogenicity, such as spatial structure and environmental heterogeneity (Sasaki *et al.*, 2002; Brown & Tellier, 2011; Tellier & Brown, 2011), are crucial for our understanding of coevolutionary dynamics; (ii) We then quantify the relative amount of variation in pathogenicity and host resistance present at spatial and temporal scales across seven wild host–pathogen systems. Using these patterns, we evaluate (a) whether the observed patterns of diversity yield support for ARD or FSD mode of coevolutionary selection, whereby high levels of within-population diversity would suggest FSD and low-level ARD, (b) whether spatial, temporal and spatiotemporal variation are important in safeguarding variation in pathogenicity, as suggested by a significant fraction of variation and level of asynchrony in pathogenicity among populations and (c) whether variation in host diversity and pathogen diversity are interrelated, as would be expected based on local coevolutionary interactions (Dybdahl & Storfer, 2003); (iii) Finally, to understand whether variation in pathogenicity is due to selectively neutral or adaptive forces (Slatkin, 1987; Thrall & Burdon, 2002), we explore patterns of pathogen local adaptation and differences between neutral and pathogenic variation (the latter is discussed in more detail in the section *Molecular and genetic variation*).

Literature search

We focused our literature review search efforts on microbial pathogens (thereby excluding animal macroparasites such as nematodes and helminths). For this purpose, we searched the Web of Science for relevant studies using combinations of search terms 'plant', 'animal', 'pathogen', 'virulence', 'infectivity', 'pathogenicity', 'aggressiveness', 'local adaptation', 'resistance', 'spatial scale' or 'spatial structure'. From each paper, we scanned references to other relevant studies, and we performed forward searches on a number of key papers. This search resulted in 48 studies covering plant (n = 42) and animal (n = 6) pathogens. Given the paucity of information on the spatial distribution of pathogenicity for animal pathogens, we focus in the main text on plant pathogens (see Box A for a comparison with animal pathogens).

Definitions

The vocabulary and definitions used in plant pathology (Vanderplank, 1968; Agrios, 2005) and animal pathology and evolutionary ecology (Read, 1994) are at least partly contradictory (cf. Sacristán & García-Arenal, 2008). To prevent confusion, we explicitly spell out our definitions. We define infectivity as the ability of the pathogen to overcome host resistance and infect a given host individual (often referred to as 'virulence' in plant pathology); aggressiveness as the extent of within-host growth; and virulence as the extent of damage to the host. As we are interested in spatial and temporal variation in both infectivity and aggressiveness, we use the term pathogenicity in those instances where we want to encompass both the qualitative (infectivity) and quantitative (aggressiveness) aspects of pathogen fitness.

How is variation in pathogenicity measured?

Reciprocal transplant experiments

These are characterized by planting a range of host genotypes from a number of different locations into all those locations (i.e. all sympatric and allopatric combinations), recognizing that each location is likely to be characterized by a distinct pathogen community. Interpretation of the results of reciprocal transplant experiments can be confounded by among-location environmental differences in addition to variation in the structure of the pathogen population. However, an advantage of field transplant experiments is that estimates of pathogenicity reflect both natural encounter rates and infection outcomes between specific host and pathogen genotypes (Burdon, 1987; Nuismer & Gandon, 2008). Hence, experimental results may be more likely to reflect host–pathogen dynamics that play

out in the field compared with results obtained from controlled inoculation experiments.

Cross-inoculations

In many plant pathogen studies, a set of host lines known to differ in resistance phenotype (a 'differential set') is inoculated separately with a series of different pathogen isolates in a common environment. As the host lines are specifically selected for their differential response to individual pathogen isolates, such an approach is likely to detect a large number of pathotypes with different infectivity patterns. However, as the host lines in the differential set are frequently collected from a much broader geographical area than the pathogen, the host–pathogen interaction may at least partly be taken out of its ecological and evolutionary context, and the variation observed may be functionally irrelevant or hard to interpret. For example, Antonovics *et al.* (2011) showed that the interaction outcome (resistance, partial resistance, susceptible) of hosts inoculated with local (sympatric) pathogens differs from those inoculated with allopatric pathogens, with a larger fraction of hosts showing partial resistance to local pathogens.

Unfortunately, results from common garden and cross-inoculation approaches can be hard to reconcile. As such, a combination of laboratory inoculation experiments and common garden field experiments may be useful in attempting to disentangle the contribution of encounter rate and encounter outcome in natural settings. Using these two approaches, Alexander (1989) and Alexander *et al.* (1993) showed that infection of *Silene alba* by *Microbotryum violaceum* is dependent on both floral phenology (encounter frequency) and genotype-dependent interactions (encounter outcome). Likewise, other studies involving the same host–pathogen interaction have shown that plant height and floral abundance (Alexander *et al.*, 1984; Thrall & Jarosz, 1994) correlate with the likelihood of infection. It is likely that less studied features, such as intraspecific variation in pathogen traits (e.g. the timing of sporulation), may also affect the frequency of interactions between specific host and pathogen genotypes.

Another challenge in these studies is that the pathogen may simultaneously evolve in response to the host population, the environment and possibly the interaction between host genotype and the environment (Laine, 2008; Wolinska & King, 2009). In such cases, measuring local adaptation in a common environment (such as the laboratory or greenhouse) may not reflect adaptation measured in the field (Laine, 2007; Ridenhour & Nuismer, 2007).

Molecular and genetic variation

The genetic structure of many pathogen populations has been elucidated by targeting underlying neutral genetic variation. In addition to using neutral genetic markers, several recent studies have also targeted genetic variation in genes involved in the infection process ('resistance' and 'avirulence' genes; Barrett *et al.*, 2009b). In combination with phenotypic resistance and infectivity data, such molecular data can provide powerful insight into the forces structuring both host and pathogen populations. For example, the spatial structure of neutral genetic variation – as compared to variation in phenotypes or functional genes – can give insight into the strength and sign of selective forces (Merilä & Crnokrak, 2001; Jorgensen *et al.*, 2006; Barrett *et al.*, 2008) or into the mating system of the pathogen (Barrett *et al.*, 2008). Moreover, analysis of patterns of variation in coding sequences (e.g. the ratio of synonymous vs. nonsynonymous mutations) underlying variation in resistance or pathogenicity can provide powerful insight into long-term patterns of evolution in populations (e.g. the importance of genetic arms races vs. balancing selection; Barrett *et al.*, 2009b).

The spatial scale of variation in pathogenicity

Strikingly, our review of the literature (42 studies involving 25 distinct plant–pathogen associations) unambiguously demonstrates the existence of variation in pathogenicity in virtually all study systems and at spatial scales ranging from single host individuals to entire regions spanning hundreds of kilometres (Table 1; see Box A for a comparison with animal pathogen studies). Variation in infectivity among pathogen isolates was omnipresent, where each study system contained multiple pathogen strains that varied in their ability to infect different host plant genotypes.

Variation in pathogenicity within hosts

The issue of multiple infections (i.e. superinfection) within single host individuals has been a topic of considerable interest for studies of human–parasite and animal–parasite interactions (Anderson *et al.*, 1995; Torres, 1996; Al-Yaman *et al.*, 1997; Butto *et al.*, 1997; Huo *et al.*, 1997; Ebert, 1998; Read & Taylor, 2001; Theron *et al.*, 2004; Pisoni *et al.*, 2007), in part because of the implications for how within-host competition among pathogen strains might influence the evolution of virulence (Lipsitch & Moxon, 1997). Although this issue has only recently gained widespread interest among plant pathologists, the few studies to date suggest that co-infection is also common in natural plant pathosystems (de Nooij & van Damme, 1988b; Wille *et al.*, 2002; Hood, 2003; Capelle & Neema, 2005; Ganz & Washburn, 2006; López-Villavicencio *et al.*, 2007). Likewise, studies in agricultural systems frequently show a high rate of co-infection (Keller *et al.*, 1997; McDonald *et al.*, 1999; Linde *et al.*, 2002). Although

Table 1 A list of studies assessing the spatial scale of variation in pathogenicity in wild plant–pathogen interactions.

Reference	Species	No. pathogen populations	Spatial scale (min. and max. distance separating pathogen populations, km)	How pathogenicity is measured	At what scale variation in pathogenicity is detected
Alexander (1989)	*Silene latifolia* (white campion)–*Microbotryum violaceum* (anther-smut fungus)	1	Single population	Inoculations	Within population
Alexander *et al.* (1993)	*Silene latifolia* (white campion)–*Microbotryum violaceum* (anther-smut fungus)	1	Single population	Inoculations	No variation within population
Barrett *et al.* (2009b)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	10	0.5–320	Avr genes	Within and between populations
Bevan *et al.* (1993b)	*Senecio vulgaris* (groundsel)–*Erysiphe fischeri* (powdery mildew fungus)	2	480	Inoculations	Within and between populations
Burdon & Jarosz (1991)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	1	Single population	Inoculations	Within population
Burdon & Jarosz (1992)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	9	0.3–110	Inoculations	Within and between populations
Burdon *et al.* (1999)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	4	0.2–265	Inoculations	Within and between populations and between metapopulations
Burdon *et al.* (2002)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	37	4–3310	Inoculations	Continental
Capelle & Neema (2005)	*Phaseolus vulgaris* (common bean)–*Colletotrichum lindemuthianum* (fungal pathogen)	1	Single population (3–500 m)	Inoculations	Within host and Within population
Carlsson-Granér (1997)	*Silene dioica* (red campion)–*Microbotryum violaceum* (anther-smut fungus)	3	< 10	Common gardens	Between populations (within population not tested)
Carlsson-Granér *et al.* (1999)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	3	0.1	Inoculations	Within and between populations
Davelos *et al.* (1996)	*Spartina pectinata–Puccinia seymouriana* and *Puccinia sparganioides* (rust fungi)	3	0.2–4.5	Inoculations and common gardens	Between populations (within population not tested)
de Nooij & van Damme (1988b)	*Plantago lanceolata* (ribwort plantain)–*Phomopsis subordinaria* (fungal pathogen)	3	40–110	Inoculations	Within hosts, within and between populations
Ennos & McConnell (1995)	*Pinus sylvestris* (Scots pine)–*Crumenulopsis sororia* (fungal canker)	3	60–120	Inoculations	Between populations (within population not tested)
Ericson *et al.* (2002)	*Filipendula ulmaria* (meadowsweet)–*Triphragmium ulmariae* (rust fungus)	4	3–350	Inoculations	Between populations (within population not tested)
Espiau *et al.* (1998)	*Chondrilla juncea* (skeletonweed)–*Puccinia chondrillina* (rust fungus)	1	Single population	Inoculations	Within population
French & Manion (1975)	*Populus tremuloides* (quaking aspen)–*Hypoxylon mammatum* (fungal canker)	1	Single population	Inoculations	Within population
Geffroy *et al.* (1999)	*Phaseolus vulgaris* (common bean)–*Colletotrichum lindemuthianum* (fungal pathogen)	3	*c.* 3000–6500	Inoculations	Continental
Gérard *et al.* (2006)	*Populus nigra* (black poplar)–*Melampsora larici-populina* (rust fungus)	5	8–93	Inoculations	Within and between populations
Goss & Bergelson (2006)	*Arabidopsis thaliana–Pseudomonas viridiflava* (foliar bacterial pathogen)	5	8–95	Inoculations	Within and between populations
Jarosz & Burdon (1991)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	10	0.3–100	Inoculations	Within and between populations

Table 1. ***(Continued)***

Reference	Species	No. pathogen populations	Spatial scale (min. and max. distance separating pathogen populations, km)	How pathogenicity is measured	At what scale variation in pathogenicity is detected
Kaltz & Shykoff (2002)	*Silene latifolia* (white campion)–*Microbotryum violaceum* (anther-smut fungus)	4	17–114	Inoculations	Within and between populations
Kaltz *et al.* (1999)	*Silene latifolia* (white campion)–*Microbotryum violaceum* (anther-smut fungus)	14	2–166	Inoculations	Within and between populations
Kinloch & Stonecypher (1969)	*Pinus taeda* (loblolly pine)–*Cronartium fusiforme* (fusiform rust)	6	0–3.6	Common gardens	Between populations (within population not tested)
Laine (2005)	*Plantago lanceolata* (ribwort plantain)–*Podosphaera plantaginis* (fungal pathogen)	4	13–43	Inoculations	Between populations
Lebeda & Petrželová (2004)	*Lactuca serriola* (prickly lettuce)–*Bremia lactucae* (lettuce downy mildew)	78	*c.* 0.1–300	Inoculations	Within and between populations
Lenné & Burdon (1990)	*Stylosanthes guianensis* (common stylo)–*Colletotrichum gloeosporioides* (anthracnose)	5	Single population (for each of five populations)	Inoculations	Within population
Meyer *et al.* (2001)	*Bromus tectorum* (cheatgrass)–*Ustilago bullata* (head smut fungus)	4	*c.* 40–600	Inoculations	Within and between populations
Meyer *et al.* (2005)	*Bromus tectorum* (cheatgrass)–*Ustilago bullata* (head smut fungus)	4	*c.* 40–600	Inoculations	Within and between populations
Miles & Lenné (1984)	*Stylosanthes guianensis* (common stylo)–*Colletotrichum gloeosporioides* (anthracnose)	1	Single population	Inoculations	Within population
Niemi *et al.* (2006)	*Salix triandra* (almond willow)–*Melampsora amygdalinae* (rust fungus)	4	355–907	Inoculations	Within and between populations
Oates *et al.* (1983)	*Avena barbata, A. fatua* and *A. ludoviciana*–*P. coronata* and *P. graminis*	248	Across the state of New South Wales, Australia	Inoculations	Regional
Parker (1988)	*Amphicarpaea bracteata* (hog peanut)–*Synchytrium decipiens* (fungal pathogen)	1	Single population	Inoculations	Within population
Parker (1989)	*Podophyllum peltatum* (mayapple)–*Puccinia podophylli* (rust fungus)	6	*c.* 0.7–48	Reciprocal common gardens	Between populations
Roslin *et al.* (2007)	*Quercus robur* (pedunculate oak)–*Erysiphe alphitoides* (oak powdery mildew)	4	0.3–1.8	Inoculations	Within population
Roy (1998)	*Arabis holboellii* (rockcress)–*Puccinia monoica* and *P. thlaspeos* (rust fungi)	3	*c.* 25–40	Reciprocal common gardens	Between populations
Sicard *et al.* (1997a)	*Phaseolus vulgaris* (common bean)–*Colletotrichum lindemuthianum* (fungal pathogen)	5	40–385	Inoculations & ITS/ RAPD	Within and between populations
Sicard *et al.* (1997b)	*Phaseolus vulgaris* (common bean)–*Colletotrichum lindemuthianum* (fungal pathogen)	3	*c.* 3000–6500	Molecular (RAPD; ITS) and inoculations	Continental
Sicard *et al.* (2007)	*Phaseolus vulgaris* (common bean) and *P. coccineus*–*Colletotrichum lindemuthianum* (fungal pathogen)	5	5–25	Inoculations	Within and between populations
Springer (2007)	*Hesperolinon californicum* (California dwarf flax)–*Melampsora lini* (rust fungus)	10	1–80	Inoculations	Regional cline
Thrall *et al.* (2002)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	6	0.2–10	Inoculations	Within and between populations
Thrall *et al.* (2001)	*Linum marginale* (wild flax)–*Melampsora lini* (rust fungus)	16	0.1–10	Inoculations	Within and between populations

co-infection is hardly surprising, it has potentially pronounced consequences for host–parasite dynamics, with predicted effects on the evolution of virulence and transmission ability (Bull, 1994; Nowak & May, 1994; Frank, 1996; Brown *et al.*, 2002; de Roode *et al.*, 2005; Alizon & Lion, 2011; Laine, 2011).

Importantly, the presence of different strains infecting a single host increases the likelihood for the evolution and emergence of new variation in pathogenicity. For some plant pathogens, co-infection is the prerequisite of sexual reproduction, and even among asexual pathogens, co-infection promotes exchange of genetic information (e.g. by somatic exchange of genetic information; Burdon *et al.*, 1982). Furthermore, theory predicts that the existence of multiple infections may facilitate the maintenance of polymorphism in pathogenicity within local populations via competitive interactions (Levin & Pimentel, 1981; Anderson & May, 1982; Bonhoeffer & Nowak, 1994; Nowak & May, 1994; Gandon *et al.*, 2002). For example, Wille *et al.* (2002) demonstrated that the outcome of competition among endophyte genotypes can vary depending on host plant genotype, thereby demonstrating a mechanism by which host plant genetic diversity can maintain pathogen diversity. Likewise, coexistence of pathogens could be mediated by a trade-off between within-host competitive ability and other traits such as dispersal ability (Leibold & Miller, 2004) and off-host survival (Abang *et al.*, 2006; Sommerhalder *et al.*, 2011), or based on the classic hypothesis that more virulent pathogens have less potential for dispersal due to a shorter lifetime of the host, but are better within-host competitors (Anderson & May, 1982). Moreover, 'cheater' genotypes may emerge that perform better in mixed infections than in single infections (Barrett *et al.*, 2011). Finally, genetic diversity of the pathogen population may also influence the frequency at which co-infections occur. López-Villavicencio *et al.* (2007) observed that high genetic diversity within pathogen populations may result in less co-infections, seemingly due to higher within-host competitive exclusion among unrelated strains.

Variation in pathogenicity within host populations

Table 1 demonstrates that variation in pathogenicity within populations is widespread (97% or 28 out of 29 studies). As the interaction between host and pathogen is frequently genotype specific (i.e. the interaction outcome depends on both host and pathogen genotype), this strongly supports frequency-dependent maintenance of resistance and pathogenic polymorphisms within local populations. Here, the well-established theory of negative frequency-dependent selection states that rare alleles are advantageous and that fitness declines when the frequency of the allele increases (Haldane, 1949; Jayakar, 1970; Leonard, 1997; Tellier & Brown, 2007).

Although the role of negative frequency-dependent selection in maintaining diversity within pathogen populations has proven difficult to quantify unequivocally, there are a range of studies that show patterns consistent with such dynamics. For example, Chaboudez & Burdon (1995) provide convincing evidence for negative frequency-dependent dynamics, by demonstrating that locally common clones of *Chondrilla juncea* occurring in their home range in Turkey were more likely to be infected by the rust fungus *Puccinia chondrillina*. In animal host–pathogen systems, a classic example from a natural system involves a longitudinal study of macroparasitic *Microphallus* trematodes preferentially infecting locally common snail genotypes of the species *Potamopyrgus antipodarum* (Dybdahl & Lively, 1998; Lively & Dybdahl, 2000). More recently, a 6-year study of the interaction between native flax (*Linum marginale*) and its associated rust (*Melampsora lini*) strongly supports a role for reciprocal coevolution in maintaining resistance and infectivity polymorphisms via negative frequency dependence, as well as a role for trade-offs between infectivity and aggressiveness (Thrall *et al.*, 2012).

Nevertheless, convincing demonstrations of negative frequency-dependent selection still remain rare in wild host–pathogen interactions (Barrett, 1988; Roy, 1998; Decaestecker *et al.*, 2007; Meyer *et al.*, 2010). Although this lack of evidence may be due to the absence or weakness of negative frequency-dependent selection in wild host–pathogen interactions, it is equally, if not more likely, that this reflects a shortage of long-term studies in natural systems (Gandon *et al.*, 2008). Moreover, it is possible that the same system may switch between ARD and FSD, as ARD is considered difficult to maintain over time due to fitness costs and mutation limitations (Buckling & Rainey, 2002; Gómez & Buckling, 2011). Furthermore, when multiple loci are involved in the interaction, some loci may evolve according to FSD whereas others follow ARD (Gandon *et al.*, 2008). Broad-scale spatiotemporal data of natural host–pathogen interactions are required given that the effects of gene flow, genetic drift and mutation, and local extinction–recolonization processes can potentially obscure evolutionary patterns. These patterns may be further complicated given the potential for the strength and direction of selection to vary through space and time (Thompson, 2005; Smith *et al.*, 2011). Hence, an explicit consideration of the spatial structure of multiple interacting populations will be paramount in developing a quantitative understanding of the processes that drive the evolution and maintenance of diversity in pathogenicity and resistance in host–pathogen interactions (Thrall *et al.*, 2012).

Variation in pathogenicity among host populations

Variation in pathogenicity among populations is as pervasive as it is within pathogen populations (100%, or 27 out of 27 studies; Table 1). As most natural host–pathogen associations (including those listed in Table 1) are characterized by migration and gene flow among neighbouring populations within a metapopulation context (Jarosz & Burdon, 1991; Laine, 2005), assessing the role of among-population processes is critical for understanding the coevolutionary dynamics of local host–pathogen interactions. For example, given substantial variation in pathogenicity among populations, local coevolutionary outcomes will not only depend on fine-scale processes generating genetic variation (e.g. mutation, sexual recombination), but will be simultaneously fuelled by the arrival of potentially novel pathogenicity and resistance genes from neighbouring populations (Thrall & Burdon, 1997). A focus on a single population will clearly leave the researcher unable to trace the origin of new variation (e.g. whether due to local mutation or immigration); however, even when immigrant status can be attached to a new pathotype, its spatial origin (near or far) may still be undeterminable. For example, in the Australian flax–flax rust system, a 12-year annual survey of *M. lini* pathogenicity in the Kiandra population detected the appearance of a novel pathotype. Over a 3-year period, the frequency of this pathotype increased from < 1% to > 28% before suddenly disappearing entirely. Although its novelty in the Kiandra population was confirmed by its unique isozyme signature, its spatial origin was never identified (J.J. Burdon, unpublished data). Although examples from natural systems are few, studies of agricultural pathogens provide clear-cut examples of new mutations arising in response to new resistant host plant varieties, and the subsequent spread of such pathogens across large spatial scales (McDonald & Linde, 2002).

As discussed below, variation in pathogenicity among locations may be either due to neutral (e.g. due to mutation, genetic drift) or adaptive (where selection varies among populations) processes. We note that such spatially heterogeneous selection may be due to biotic (i.e. adaptation to spatially varying host plant genotypes or other members of the community) or abiotic factors. Notably, when the host evolves faster than the pathogen, variation in pathogenicity may be maladaptive (Gandon *et al.*, 1996; Kaltz & Shykoff, 1998). Moreover, immigration may result in the inflow of maladaptive genes into the local population.

Variation in pathogenicity among metapopulations (and larger spatial scales)

Given that variation among pathogen populations within metapopulations is omnipresent, it is not surprising that variation in pathogenicity is also universal at larger spatial scales (ranging from among geographical regions to intercontinental scales; 100%, or 6 of 6 studies; Table 1). For example, Burdon and colleagues have shown that pathogenic variation in wild flax rust exists across the entire Australian continent, as well as among environmentally distinct plains and mountain regions in south-eastern Australia (Burdon *et al.*, 1999, 2002). Likewise, pathogenicity of the fungal pathogen *Colletotrichum lindemuthianum* varies among three geographical areas within the range of the common bean *Phaseolus vulgaris* in Latin America (Sicard *et al.*, 1997b). These studies support the idea that coevolutionary interactions may vary across broad geographical areas (Thompson, 2005). In addition, the work of Barrett *et al.* (2008) further suggests that environmental and climatic differences between regions are likely to play a significant role with regard to maintaining variation in host and pathogen life-history traits that can markedly influence levels of diversity.

Spatial and temporal structure of variation in pathogenicity and resistance – a quantitative analysis

Although variation in pathogenicity exists both within and among populations (Table 1), a quantitative comparison of seven wild pathosystems that have been studied in detail reveals that the majority of pathogenic variation can be attributed to variation within populations (Fig. 1a). Low levels of between-population variation relative to strong genetic variation within populations suggest that local interactions are dominant. Traits under strong frequency-dependent selection are expected to show such patterns according to models by Schierup *et al.* (2000a,b). This pattern may further be shaped by the interplay between balancing selection, locally variable selection generated by G × (G ×) E interactions, replenishment of variation by frequent gene flow and possibly uniform selection across the landscape. As a consequence, genetic drift may only infrequently result in the loss of pathogenic variation within populations. Disentangling the relative importance of these factors is likely to be crucial in understanding the spatial distribution and maintenance of pathogenic polymorphisms.

Unfortunately, the role of gene flow in homogenizing populations is hard to evaluate given the lack of data across a wide range of pathosystems: although populations were generally separated by a few to hundreds of kilometres, each of the pathogens we were able to evaluate disperses aerially, likely resulting in frequent long-distance dispersal. Broadening our ability to conduct comparative studies including other disease transmission modes such as vector-dispersed (e.g. insect-transmitted floral smuts) or soil-borne pathogens will be essential if we are to further our understanding of the

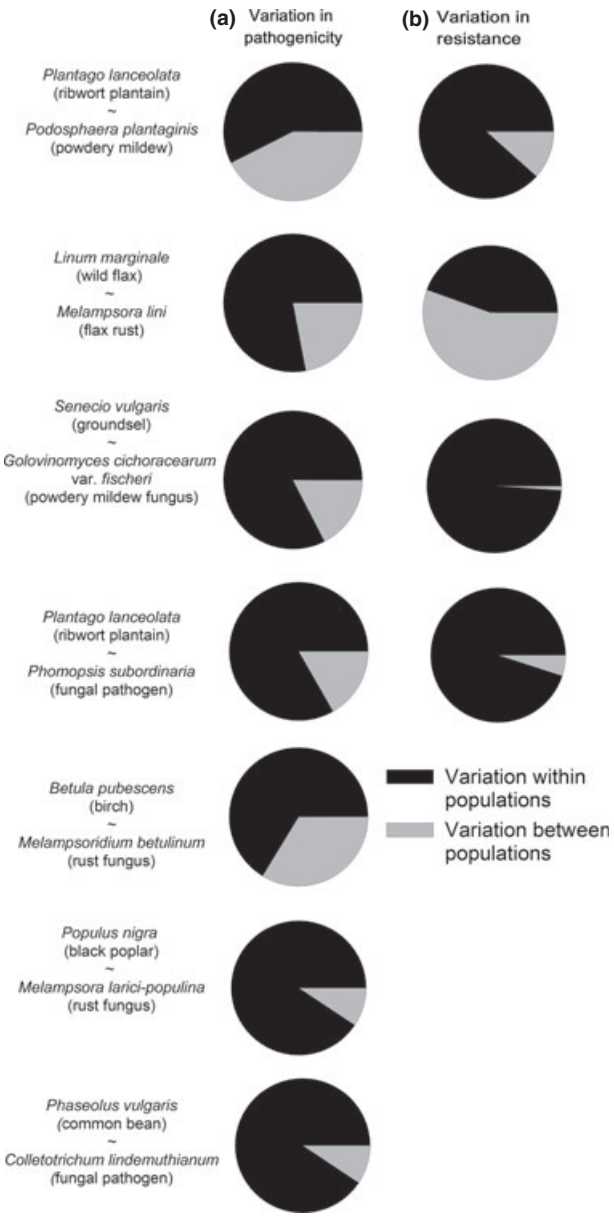

Fig. 1 The relative amount of variation in (a) pathogenicity and (b) resistance within and among populations for seven pathosystems. Multivariate analyses were conducted using pathogenicity and resistance (either binary or quantitative) as the response variable and the fixed variable *Population* as the explanatory variable (note that the residual error term reflects the within-population variation). Analyses were implemented with the function *adonis* in package VEGAN (version 1.17-6) in R (Oksanen *et al.*, 2010), a method related to the AMOVA procedure implemented by Excoffier *et al.* (1992). Data sources (and for more detailed information): *Plantago lanceolata–Podosphaera plantaginis* from Laine (2005); *Linum marginale–Melampsora lini* from Barrett *et al.* (2009b and unpublished data; data shown are from the 'Plains' metapopulation); *Senecio vulgaris–Golovinomyces cichoracearum* from Bevan *et al.*(1993a,b); *Plantago lanceolata–Phomopsis subordinaria* from de Nooij & van Damme (1988a,b); *Betula pubescens–Melampsoridium betulinum* from Ericson & Burdon (2009); *Populus nigra–Melampsora larici-populina* from the AMOVA table given in Gérard *et al.* (2006); *Phaseolus vulgaris–Colletotrichum lindemuthianum* from the AMOVA table given in Sicard *et al.* (1997a).

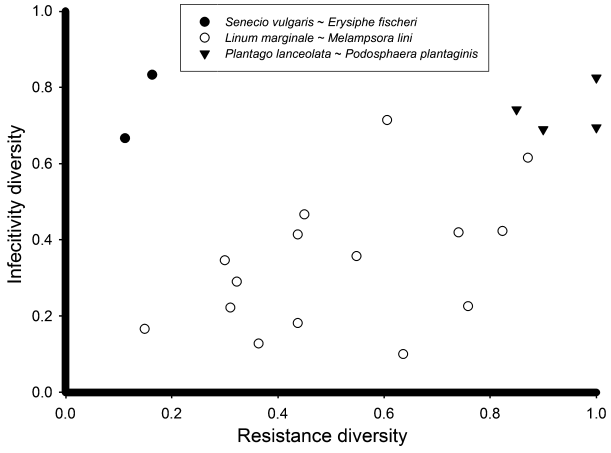

Fig. 2 Within-population diversity in pathogen infectivity and host resistance diversity are positively associated for three study systems (ANCOVA; $F_{1,17} = 4.37$; $P = 0.04$, $R^2 = 0.09$). Additional variation is explained by differences among study systems in the mean diversity in infectivity ($F_{2,17} = 14.36$; $P = 0.002$, $R^2 = 0.57$).

role of gene flow and other aspects of life history in determining the spatial scale of variation in pathogenicity.

Variation in host resistance – and its distribution within and among host populations – is likely to impact heavily on the distribution of variation in pathogenicity (and *vice versa*). For example, if patches consist of single clones, local selection is likely to be directional and may result in low within-patch pathogenic diversity. On the other hand, large variation in host resistance within populations may select for a high number of associated pathogen genotypes within host populations. Indeed, Fig. 1 shows that the distribution of host resistance shows a pattern roughly comparable to the distribution in pathogenicity, consistent with the idea that host resistance diversity is the driving force behind variation in pathogenicity. Moreover, within three natural host–pathogen study systems, there is a positive relationship between within-population diversity in infectivity and diversity in host resistance (Fig. 2). A related pattern emerges in the Australian flax–flax rust and the almond willow–rust systems, where within-population mean infectivity and mean resistance are highly correlated (Thrall & Burdon, 2003; Niemi *et al.*, 2006; but see Springer, 2007). Likewise, agricultural

studies have shown a clear-cut relationship between host plant resistance and variation in pathogenicity. For example, the diversity and identity of host plant genotypes in agricultural fields may affect infection intensity, pathogen diversity and the genotypic composition of the pathogen population (Wolfe, 1985; Zhu *et al.*, 2000; Mundt, 2002; Goyeau *et al.*, 2012).

Nevertheless, the results show some level of discrepancy between the distribution of resistance and pathogenicity: for example, the host plant *L. marginale* shows strong variation in resistance among local populations, whereas its associated rust *M. lini* is less differentiated among locations (Fig 1; Thrall *et al.*, 2001). This pattern may be explained by the large dispersal range of the pathogen as compared to the host plant (Thrall & Burdon, 1999) and is mirrored by evidence for stronger pathogen adaptation at regional as opposed to local spatial scales (Thrall *et al.*, 2002). In striking contrast, for the ribwort plantain *Plantago lanceolata* (de Nooij & van Damme, 1988a,b) and the groundsel *Senecio vulgaris* (Bevan *et al.*, 1993a,b) systems, the majority of variation in host resistance is present within populations, whereas their pathogens vary considerably more among locations (Fig. 1). Although these first quantitative studies of the spatial structure of variation in pathogenicity and host resistance provide novel insights, there is a clear need for studies of many more wild systems to generalize these patterns.

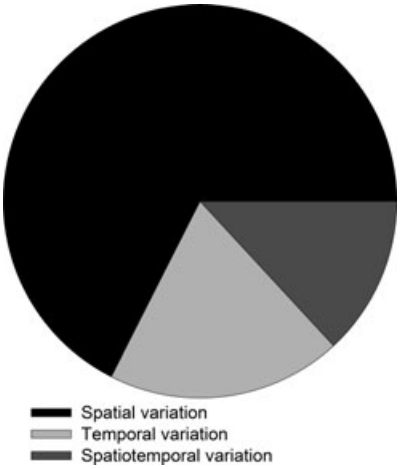

Fig. 3 Relative amount of spatial, temporal and spatiotemporal variation in pathogenicity in the wild flax–flax rust pathosystem (*Linum marginale–Melampsora lini*). Data are based on pathogen samples (n = 659) randomly collected from three populations across 12 years (1986–1997; Burdon *et al.*, unpublished data). Populations are Kiandra, P1 and P2 in Kosciuszko National Park, Australia (see Jarosz & Burdon, 1991 for a map of the populations). Pathogens were tested on a standard set of 11 *Linum marginale* host lines described by Jarosz & Burdon (1991). A multivariate analysis explained the infectivity (0/1) of the pathogen across all host lines by the variables *Population*, *Year* and the *Population* × *Year* interaction. Analyses were implemented with the function *adonis* in package VEGAN (version 1.17-6) in R (Oksanen *et al.*, 2010).

The temporal scale of variation in pathogenicity

For several decades, host–pathogen models have emphasized that variation in pathogenicity and host resistance can be maintained by (frequency-dependent) changes in allele/gene frequencies through time (Brown & Tellier, 2011). However, most empirical studies have replicated sampling across space rather than through time, based on the argument that assessment across multiple populations in space provides a reasonable surrogate for variation through time (Burdon *et al.*, 1990). Nevertheless, recent work suggests this may not always be the case. For example, Gómez & Buckling (2011) showed that although phages perform better on local than foreign bacterial hosts, it is the bacteria that are best adapted to the contemporaneous as compared to past phages. In a similar vein, the bacterial endoparasite *Pasteuria ramosa* shows no spatial adaptation (Ebert *et al.*, 1998), but it is temporally adapted to its host *Daphnia magna* (Decaestecker *et al.*, 2007). A time-shift assay of changes in resistance and infectivity within populations of *L. marginale–M. lini* demonstrated striking shifts in interaction traits at just 2-year intervals, suggesting that any assessments will be highly sensitive to the point in time the host–pathogen interaction is sampled on (Lively, 1999; Gandon *et al.*, 2008; Thrall *et al.*, 2012).

Due to the lack of published results on spatiotemporal variation in pathogenicity in natural systems, we here use a body of unpublished data generated in a long-term study of the flax rust, *M. lini*, infecting the wild flax *L. marginale* in Australia (Burdon & Jarosz, 1992; Burdon & Thompson, 1995). This 12-year sampling programme across three populations illustrates clearly that spatial variation (68% of total variation), temporal variation (19% of total variation) and the interaction between space and time (13% of total variation) all contribute to the maintenance of pathogenic polymorphisms (Fig. 3). Such spatiotemporal variation is a signature of asynchrony among populations, hence promoting the potential for pathogen local adaptation. Although comparative data are lacking, we expect that some study systems will harbour even more temporal and spatiotemporal variation, as the host populations included in the current study represented two different ecotypes (i.e. 'bog' and 'hill' sites; Carlsson-Granér *et al.*, 1999).

We note that another interesting approach would be to follow both phenotypic and genotypic changes in pathogen population structure over the course of a single epidemic during a host growing season. For example, selection for more aggressive or infective

genotypes may be predicted to be an important agent of temporal change within pathogen populations. However, the exact evolutionary trajectory may depend on the existence or strength of a trade-off between aggressiveness and infectivity (Thrall & Burdon, 2003), the frequency of recolonizations and immigration, and the diversity and average resistance of hosts.

Evidence for selection in shaping variation in pathogenicity

If variation in pathogenicity – as detected across several spatial scales (Table 1) – is adaptive, we would expect local adaptation (i.e. a better performance on the local vs. foreign host) of the pathogen to occur across each of these spatial scales. Indeed, a review of the literature shows that local adaptation is common in host–pathogen systems (Appendix S1; see also Kaltz & Shykoff, 1998; Greischar & Koskella, 2007; Hoeksema & Forde, 2008). Most importantly, local adaptation is frequently detected at each spatial scale: individual hosts (100%; 3 of 3 studies); populations (52%; 14 of 27 studies) and among regions (67%; 2 of 3 studies). Moreover, for three of the studies included in Fig. 1a, among-population variation in pathogenicity has been shown to be at least partly adaptive at multiple spatial scales (*L. marginale–M. lini*; *Plantago lanceolata–Podosphaera plantaginis*; and *P. vulgaris–C. lindemuthianum*). For example, Thrall *et al.* (2002) detected local adaptation of *M. lini* at both population and metapopulation levels. Likewise, local adaptation of the fungal pathogen *C. lindemuthianum* to the common bean *P. vulgaris* has been convincingly demonstrated at the level of the individual host plant (Capelle & Neema, 2005), population (Sicard *et al.*, 1997a) and regional scale (Sicard *et al.*, 1997b). This strongly suggests that the variation detected at each of several spatial scales may be adaptive – emphasizing the potential role for natural selection in shaping variation in pathogenicity within and among populations. Moreover, the frequent detection of local adaptation suggests that FSD may be more common than ARD.

Nevertheless, we note that a lack of local adaptation is also a common finding (Kaltz *et al.*, 1999; Goss & Bergelson, 2006). Although some studies may have failed to detect local adaptation because of inappropriate experimental designs (Kawecki & Ebert, 2004), the absence of local adaptation should be expected in many situations given the potentially cyclical nature of coevolution where hosts may gain the upper hand over their pathogens occasionally (Kaltz & Shykoff, 1998). Indeed, the occurrence and extent of local adaptation is likely to depend on the strength of selection, frequency of local extinctions (where high extinction rates preclude local adaptation) and the frequency of gene flow (where high gene flow may swamp local adaptation; Slatkin, 1987; Tack & Roslin, 2010). Moreover, pathogen and host life-history features (such as dis-

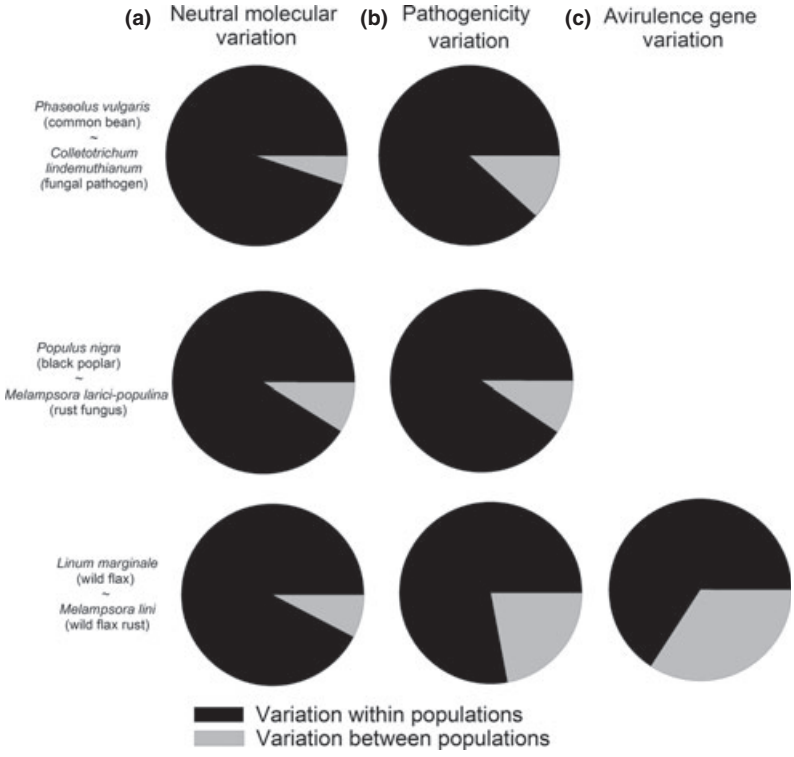

Fig. 4 Spatial scale of variation in the pathogen: (a) neutral genetic variation, (b) pathogenicity and (c) genetic variation in avirulence genes. Multivariate analyses were conducted using the response variables pathogenicity (0/1), RAFLP markers (0/1) and avr alleles (0/1). The explanatory variable was *Population*, and the residual error term reflects the within-population variation. Analyses were implemented with the function *adonis* in package VEGAN (version 1.17-6) in R (Oksanen *et al.*, 2010). Data sources (and for more detailed information): *Phaseolus vulgaris–Colletotrichum lindemuthianum* from AMOVA table given in Sicard *et al.* (1997a); *Populus nigra–Melampsora larici-populina* from AMOVA table given in Gérard *et al.* (2006); *Linum marginale–Melampsora lini* from Barrett *et al.* (2009b).

persal ability, host specialization and generation time) will play a crucial role in which species will be ahead in the coevolutionary race (Kaltz & Shykoff, 1998; Lajeunesse & Forbes, 2002; Greischar & Koskella, 2007; Hoeksema & Forde, 2008).

The above examples are based on cross-infection and reciprocal transplant studies. The sign and strength of selection may – for sexually reproducing species – also be inferred from a comparison of patterns of neutral and pathogenic variation among populations. For example, if variation in pathogenicity among populations is driven largely by neutral processes (i.e. mutation and genetic drift), we may expect a match in the amount of differentiation among populations as measured by putatively neutral genetic (e.g. microsatellite markers) and phenotypic variation in pathogenicity (Merilä & Crnokrak, 2001). In contrast, discrepancies between the degree of pathogenic and neutral differentiation may reflect either homogeneous selection across populations (neutral variation among populations > pathogenic variation among populations) or divergent selection (neutral variation among populations < pathogenic variation among populations). Strikingly, two of the three studies in which this can be assessed support the occurrence of divergent host-mediated selection (Fig. 4). Thus, Sicard *et al.* (1997a,b), in a study of the fungal pathogen *C. lindemuthianum* attacking common bean *P. vulgaris*, detected increased differentiation at pathogenic markers compared to neutral genetic markers among populations, suggesting that local selection pressures are important to structure pathogenicity across the metapopulation. Likewise, populations of flax rust *M. lini* attacking wild flax *L. marginale* in Australia show generally more divergence in pathogenicity traits and avirulence gene polymorphisms compared with neutral genetic variation (AFLP markers; Barrett *et al.*, 2009b; Fig. 4).

Discussion and future directions

This review on variation in pathogenicity in wild host–pathogen systems highlights several general conclusions. First, we show that variation in pathogenicity is ubiquitous across space, ranging from single hosts through patches and metapopulations to entire continents (Table 1). Importantly, this suggests that factors promoting the maintenance of pathogenic polymorphisms – such as spatial structure, environmental heterogeneity and gene complexity – play a crucial role in host–pathogen interactions. Second, we demonstrate that much variation in pathogenicity and host resistance is present within populations, thereby indicating the importance of local interactions and FSD. Nevertheless, a significant fraction of variation is present among populations and through time (Figs 1 and 3), likely playing a crucial role in safeguarding the maintenance of genetic variation within the pathosystem. Moreover, the interrelationship between host resistance and pathogenicity suggests that coevolutionary interactions are important in the maintenance of polymorphisms. Finally, at least some part of the variation in pathogenicity at each spatial scale is – in a large fraction of the study systems – adaptive, as illustrated by the frequent detection of local adaptation at each spatial scale (Appendix S1) and, to a lesser extent, a comparison of neutral and pathogenic variation (Fig. 4). The consistent maintenance of variation within populations and frequent local adaptation provide some evidence that FSD may be more common in wild host–pathogen systems than ARD. At the same time, we see several gaps and promising directions for future research.

First, environmental variation may be a crucial factor in maintaining the variation in resistance and pathogenicity that we observed, as several recent studies have shown how spatial (Gavrilets & Michalakis, 2008; Laine & Tellier, 2008; Tellier & Brown, 2011) and temporal (Mostowy & Engelstädter, 2011) heterogeneity may maintain polymorphisms. The effect of spatial and temporal heterogeneity on pathogen prevalence is indeed well described (Schnathorst, 1965; Duniway, 1979; Burdon, 1987). Moreover, recent experiments have indicated the occurrence of genotype-by-environment interactions (i.e. $G_{host} \times E$, $G_{pathogen} \times E$, or $G_{host} \times G_{pathogen} \times E$) in host–parasite systems (Laine, 2008; Vale & Little, 2009; Wolinska & King, 2009; Bryner & Rigling, 2011; Sadd, 2011; Hall & Ebert, 2012). Hence, although many of the studies in Table 1 have conducted experiments in a single controlled environment, interactions may be more variable across environments than previously realized. Moreover, environmentally mediated trade-offs between different fitness traits (e.g. infectivity, aggressiveness, survival between epidemics and transmission ability; Koskela *et al.*, 2000; Dybdahl & Storfer, 2003; Hatcher *et al.*, 2005; Abang *et al.*, 2006; Refardt & Ebert, 2007; Wolinska & King, 2009; Barrett *et al.*, 2011; Sommerhalder *et al.*, 2011), or spatially varying costs in resistance and pathogenicity (Gavrilets & Michalakis, 2008; Tellier & Brown, 2011), may well maintain population-level variation in infectivity and aggressiveness.

Second, the current focus on specialist and aerially dispersed pathogens (Table 1; Fig. 1) hinders any strong generalizations across the notoriously diverse array of host and parasite life histories. Most strikingly, appropriate data on soil-borne and vector-transmitted pathogens, generalist pathogens (Barrett *et al.*, 2009a) and viruses (Fraile & García-Arenal, 2010) are lacking (or scarce) for natural pathosystems. New data across a broad suite of study systems would help unravel the contributions of different host and pathogen life-history traits to generating patterns of variation in resistance and pathogenicity at different spatial and temporal scales. Moreover, recent developments in animal pathogen studies provide a promising starting

point for future comparisons across a wide range of organisms.

Third, much is to be gained from integrating the rapidly advancing understanding of molecular interactions governing pathogen infectivity and aggressiveness with studies of ecological genetics in wild pathogen systems (Burdon & Thrall, 2009; Fraile & García-Arenal, 2010). For example, work on the interaction between flax rust *M. lini* and its domesticated host (*Linum ussitissimum*) revealed divergent selection on avirulence genes (as based on a high ratio of nonsynonymous to synonymous mutations; Dodds *et al.*, 2006). Similar patterns have been observed in preliminary studies of the wild host *L. marginale* (Barrett *et al.*, 2008). Interestingly, the application of this molecular knowledge and approach to the dynamics of the flax rust–wild flax interaction revealed temporal variation in allele frequencies within populations, with evidence for negative frequency-dependent selection varying across populations and years (Thrall *et al.*, 2012).

Finally, the overwhelming evidence from natural systems is that hosts are attacked by a whole array of parasite species – either at the same time or physically separated in space and time (Agrios, 2005). Crucially, several studies suggest that the community members do not act in isolation, thereby necessitating a community genetics perspective to understand host–parasite interactions (Thrall *et al.*, 2007; Telfer *et al.*, 2010).

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 A list of studies assessing the spatial scale of pathogen local adaptation.

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