MINI REVIEW

The evolutionary significance of parasitism: do parasite-driven genetic dynamics occur *ex silico*?

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Abstract

It has long been recognized that reciprocal antagonism might lock host and parasite populations into a process of constant change, adapting and reacting in open-ended coevolution. A significant body of theory supports this intuition: dynamic genetic polymorphisms are a common outcome of computer simulations of host–parasite coevolution. These *in silico* experiments have also shown that dynamical interactions could be responsible for high levels of genetic diversity in host populations, and even be the principle determinant of rates of genetic recombination and sexuality. The evolutionary significance of parasitism depends on the strength and prevalence of parasite-mediated selection in nature. Here I appraise whether parasitism is a pervasive agent of evolutionary change by detailing empirical evidence for selection. Although there is considerable evidence of genetic variation for resistance, and hence the potential for selection, direct observation of parasite-driven genetic change is lacking.

Introduction

The significance of parasitism

Parasitism (including pathogens, pests and infectious disease) can be a powerful determinant of host survival and reproduction, as evidenced by the impact of pathogenic fungal outbreaks on plants (e.g. Van Alfen *et al.*, 1975), parasite-mediated population cycles (e.g. Hudson *et al.*, 1998), or the success of some biological control programs (e.g. Fenner & Ratcliffe, 1965), to give just a few examples. Although it is clear that biological enemies are both ubiquitous and can affect host population sizes, the nature of genetic interactions between host populations and their parasites, and hence the evolutionary significance of parasitism, is less clear. Certainly, parasites are evolving: new crop varieties must frequently be introduced as older ones become susceptible to evolving pest populations (Maxwell & Jennings, 1983), new diseases emerge and mutate [e.g. AIDS (Yamaguchi & Gojobori, 1997)], and the genetic make-up of more traditional diseases is continually refashioned [e.g. influenza (Fitch *et al.*, 1997), malaria (Hughes, 1991)]. Although hosts may not evolve as rapidly or as obviously as their diseases, there is evidence that the genetic structure of host populations is affected by disease. For example, natural or feral populations can evolve resistance to introduced diseases (Fenner & Ratcliffe, 1965; Warner, 1968; van Riper *et al.*, 1986), and the geographical overlap of virulence and resistance variants points to evolution in response to endemic biological enemies (e.g. Berenbaum & Zangerl, 1998; Gilbert *et al.*, 1998).

Understanding the relationship between disease, genetic variation and evolution has great importance for a variety of scientific fields, both applied and basic. First, that interactions are reciprocal implies that host genetics can determine the incidence and severity of disease, and thus a deep understanding of the genetics of coevolution stands to enhance utilitarian understanding of the conditions which mediate the damaging effects of disease and pests. Secondly, the impact of disease on the genetics of host populations is thought to have broad evolutionary implications, and it has been argued that parasitism

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may be at the heart of some lingering problems in evolutionary biology. In particular, theoretical studies have suggested that frequency-dependent selection on host and parasite genetic polymorphisms may maintain genetic variation and promote sexual reproduction (the Red Queen hypothesis) (Haldane, 1949; Levin, 1975; Jaenike, 1978; Hamilton, 1980). The maintenance of polymorphism via parasitism may also occur through balancing selection that might, for example, account for the striking polymorphism of the vertebrate immune system (Apanius *et al*., 1997).

The influence of parasitism on host genetic structure will be determined by the differential reproductive success of infected vs. uninfected host genotypes. The evolutionary significance of parasitism therefore depends on the strength and prevalence of parasite-mediated selection in nature. For some theories of disease and evolution, selection must proceed in a dynamic frequency-dependent manner and many computer simulations (i.e. *in silico* experiments) have demonstrated the plausibility of this (e.g. Hamilton *et al*., 1990). Some theorists, however, have argued that the conditions required to achieve on-going coevolution are so restrictive as to apply to few, if any, real host–parasite systems (May & Anderson, 1983; Stenseth & Smith, 1984; Kondrashov, 1993). Under this view, bursts of coevolution are rare and or at best transitory, with alleles being rapidly fixed or lost so that coevolution grinds to a halt. Ultimately, it must be determined whether parasite-driven dynamics occur *ex silico* in nature. To help assess the evolutionary significance of parasitism, here I review what is known about parasite-mediated selection in the wild. By classifying the types of investigations which have dominated research on selection, I highlight where knowledge gaps are conspicuous. The focus is on host evolution in natural populations, although mention of the parasite half of the coevolutionary interaction must inevitably slip in, as must frequent mention of agricultural/artificial systems because so much is known from them.

The evidence for selection

For parasite-mediated natural selection to occur, two criteria must be met. First, infection must reduce host reproduction or survival, and this has been amply demonstrated (Tompkins & Begon, 1999). Secondly host genotypes must differ in their susceptibility, so that parasitic infection is borne disproportionately by the susceptible subset of the population. If these assumptions are met, all else being equal, parasite-mediated changes in gene frequencies are predicted. Therefore, the study of parasite-mediated selection, in parallel with studies of natural selection generally, has concerned itself with characterizing genetic variation for host resistance, or investigating gene frequency changes over time.

Genetic variation for resistance

Genetic variation for resistance within populations is a central assumption of models of coevolution, and it has been investigated in two main ways. I distinguish between (1) those studies which measured genetic variation for resistance or heritability of resistance traits using strictly controlled exposure to parasites (common garden experiments), and (2) field studies that measured genetic correlates of infection when infection occurred under natural conditions.

Common garden

These experiments have been widely applied to reveal the potential for microevolutionary change. Plant-pathogen systems (reviewed in Thompson & Burdon, 1992) have received the most attention, but where experimental genetic analyses have been carried out on animal systems, these have also revealed substantial resistance-variation (Henter & Via, 1995; Ebert *et al*., 1998; Webster & Woolhouse, 1998). The main advantage of the 'common garden' approach is the ability to control for confounding environmental factors and accurately determine whether resistance has a strict genetic component.

However, the nature of this genetic component may not always be clear. In some cases the genetic variation revealed may be of a general form, for example because of genetic damage, that is, susceptible strains may be those with a greater load of deleterious mutations and their relatively poor condition makes them susceptible to infection. In many common garden experiments, this form of resistance cannot be distinguished from specific forms of resistance based on allelic variation at loci of major effect. Coevolutionary outcomes depend on the underlying genetic control of resistance, and frequency-dependent allele frequency fluctuations are more likely to result from specific forms of resistance (Frank, 1993; Parker, 1994). Required are studies which simultaneously examine variation in host resistance and parasite infectivity within populations to *explicitly* test for genotype specific host–parasite interactions, that is, to test if the susceptibility of a particular host genotype is dependent on which parasite genotype it encounters and if the infectivity of a particular parasite strain depends on which host genotype it encounters (e.g. Wedekind & Ruetschi, 2000; Carius *et al*., 2001). Such interactions are a key requirement for frequency-dependent selection, through which genetic variation may be maintained. Equally important is knowledge of the full range of specificities present within populations. The occurrence of host strains resistant to all pathogen strains in the population, or pathogen strains universally infective on all host strains is not conducive to frequency dependent dynamics (Carius *et al*., 2001).

By far the most work investigating the nature of host–parasite specificity has been performed on plant-pathogen

systems, where breeding experiments have shown that resistance is frequently controlled by major genes with the so-called gene-for-gene pattern of specificity (reviewed in Thompson & Burdon, 1992). Comparable studies on animals are rare, and whereas some have indicated considerable specificity (e.g. Wedekind & Ruetschi, 2000; Carius *et al*., 2001) and/or an effect of major genes (Hatchet & Gallun, 1970; Gulland *et al*., 1993; Orr & Irving, 1997), others have indicated that the control of resistance is likely to be polygenic (Sorci *et al*., 1997; Kraaijeveld *et al*., 1998).

Common garden studies are, of course, not meant to represent the uncertainties of the field. The extent to which environmental factors, which are undoubtedly consequential for disease transmission (Blower & Roughgarden, 1989; Grosholz, 1994; Smith *et al*., 1999), may swamp the genetic aspects of infection is indicated by cases where the results of common garden experiments were extended to the field. For example, Scott (1991) showed that two strains of mice which differed in their susceptibility to a nematode under controlled laboratory conditions showed no differences when infection occurred under seminatural conditions. Similarly, for a *Daphnia*-microparasite system, Little & Ebert (2000a) provided an example where genetic variation for resistance (as detected in a common garden experiment) apparently did not determine disease patterns in the field. In other populations of the same *Daphnia* study it appeared that host genetics were a determinant of natural disease patterns, but studies on other taxa are needed to establish the extent to which parasitic infections under natural conditions are influenced by the strict genetic factors revealed in common garden infections.

Field measurements

Field studies of genetic variation for resistance have demonstrated that natural infections are nonrandomly distributed among relatives (Chan *et al*., 1994; Smith *et al*., 1999; Williams-Blangero *et al*., 1999) or genotypes identified by molecular tools (e.g. Parker, 1988; Hill *et al*., 1991; Gulland *et al*., 1993; Roy & Bierzychudek, 1993; Chaboudez & Burdon, 1995; Ruwende *et al*., 1995; Gilbert *et al*., 1998; Jeffery *et al*., 1999). For studies using molecular markers, a distinction can be made between those which assayed genes likely to be directly involved in resistance (Hill *et al*., 1991; Ruwende *et al*., 1995; Gilbert *et al*., 1998) and those studies which examined neutral genes thought to be in linkage disequilibrium with resistance loci (e.g. Roy & Bierzychudek, 1993; Little & Ebert, 1999). The latter approach relies on nonrandom associations between marker loci and loci under selection (see Little & Ebert, 2000b), and thus will only be effective when linkage disequilibrium is high, for example, because of reproductive mode (but see Kohn *et al*., 2000). Studies that calculated heritabilities from analysis of relatives did so either by using pedigree data (Smith *et al*., 1999) or performing manipulations which permitted heritability calculations. For example, Grosholz (1994) provided evidence for significant heritability of a mollusc's resistance to trematode infection by marking and outplanting hosts of known relatedness and then recording the incidence of infection after a 2 month period in enclosures (see also Møller, 1990; Boulinier *et al*., 1997).

In contrast to common garden experiments, when comparing among infected and uninfected hosts in field samples it is difficult to separate the strict genetic component of resistance from condition-based effects which affect susceptibility. For example, for studies which manipulate hosts so that heritabilities can be calculated, it may be challenging to control for maternal effects which influence whether infections establish once hosts are exposed to parasites (e.g. Boulinier *et al*., 1997). In addition, field studies typically lack the control needed to determine if some genotypes are more often infected because they have a higher encounter rate with the disease, but are not more susceptible *per se*. For example, within-population spatial structuring of both host genotypes and parasite prevalences will lead to the overinfection of certain genotypes although they may not differ under controlled exposure (Little & Ebert, 1999). The importance of distinguishing between the genetic profile of hosts and the factors, genetic or otherwise, influencing the host–parasite encounter rate has been stressed (Combes, 1991; Seymour, 1995; Little & Ebert, 2000a), and clearly should matter for evolutionary biologists seeking to determine the genes upon which selection is acting. Certainly for parasitologists this is not a trivial issue. Understanding the cause of infection is key to developing rational control strategies (Bundy & Medley, 1992; Chan *et al*., 1994; Williams-Blangero *et al*., 1999).

In conclusion, studies of resistance variation have revealed considerable potential for parasite-mediated natural selection, and thus one of the main assumption underlying models of coevolution appears to be met. Knowledge gaps remain, however, and it will be helpful to have more studies which (1) investigate specificity and identify genes under selection, (2) accurately partition the components of variance in the wild (e.g. Grosholz, 1994), (3) compare, for the same genotypes, results obtained under controlled conditions with those obtained in a natural setting (e.g. Scott, 1991), and (4) test if molecular marker-based field patterns stand up under controlled exposure (e.g. Dybdahl & Lively, 1998).

Gene frequency changes

Given sufficient parasite prevalence and virulence, the simplified prediction which stems from observations of genetic variation for resistance is that gene frequencies or heritable phenotypes should change accordingly – overinfected genotypes ought to decline in frequency, the genes in healthy hosts ought to flourish. There is considerable indirect evidence that populations and

genes have been under selection, but directly linking resistance-variation to change, that is, directly observing responses to selection, has proven difficult.

Indirect evidence. Rapid evolution and certain forms of selection are thought to leave a signature on populations. Among populations, evidence for parasite evolution is observed as local adaptation of the parasite (reviewed in Kaltz & Shykoff, 1998), whereas evidence for coevolution comes from the concordant geographical distribution of virulence and resistance variants (Berenbaum & Zangerl, 1998). Chaboudez & Burdon (1995) specifically sought to infer the occurrence of frequency-dependent selection from spatial patterns of infection. They documented the regular overinfection of common genotypes in populations of a plant-pathogen system, and interpreted this to mean that parasites adapt to common genotypes, thereby providing an advantage to rarer types. The overinfection of common clones, however, was not a consistent feature of other plant-pathogen systems (Jarosz & Burdon, 1991), Daphnia–microparasite interactions (Little & Ebert, 1999), or a snail-trematode system (Dybdahl & Lively, 1995). In addition, the detailed studies of spatial patterns by Jarosz & Burdon (1991) showed no evidence that the genetic composition of local host populations determined which pathogen races were locally abundant. Undoubtedly, resistance genes detected in the greenhouse are not the only factor shaping the genetic composition of host and parasite populations. Even assuming host genetics to be the sole factor of effect, a lack of correlation between commonness and infection cannot be taken as evidence against the presence of frequency-dependent selection, because, given the appropriate time lag between the evolution of resistance in hosts and counteradaptation of parasites, many patterns are consistent with the expectations of frequency dependent selection (Dybdahl & Lively, 1995; Frank, 1996).

The occurrence of selection or arms races may also be stamped on gene sequences. A gene is generally considered to have been under positive selection when the rate of nonsynonymous nucleotide substitutions (K_a: nucleotide substitutions which result in an amino acid substitutions) is higher than the rate of synonymous substitutions (K_s: nucleotide substitutions which do not result in an amino acid substitution). Evidence for positive selection has been revealed in the immunogenic regions of both plant and animal pathogens (e.g. Hughes, 1991). On the host side, there is evidence from plant-pathogen systems that loci involved in either pathogen recognition or pathogen destruction show elevated rates of nonsynonymous substitution (McDowell *et al*., 1998; Bishop *et al*., 2000). Balancing selection has also been inferred from gene sequences. In particular, major histocompatibility (MHC) loci in humans and mice show elevated rates of nonsynonymous substitutions at antigen recognition sites, long persistence of allelic lineages and linkage disequilibrium consistent with the occurrence of overdominance, although the hypothesis of frequency-dependent selection at MHC loci has also been supported (summarized in Satta *et al*., 1994; Li, 1997).

Frequency dependent selection (FDS) can take various forms. FDS may involve the selective advantage of individuals carrying a newly arisen mutant allele and a constant turnover of alleles as mutants rise to fixation. This hypothesis is often referred to as an arms race, but it does not predict the high levels of polymorphism or the persistence of allelic lineages at MHC loci. Alternatively, and possibly applicable to the MHC case, frequency dependent selection may prevent the loss of rare variants, resulting in the long term coexistence of alleles whose frequencies fluctuate over time in a cyclical manner. A variation on this pattern, termed 'trench warfare', seems to apply to *Rpm1* gene which allows *Arabidopsis thaliana* to recognize pseudomonas pathogens (Stahl *et al*., 1999). Molecular work has indicated that resistance and susceptibility alleles at *Rpm1* have coexisted for millions of years, with pathogen advance occurring during periods where susceptibility alleles are common and pathogen retreat occurring when resistance alleles re-invade.

Estimates of selection intensities from sequence data have indicated that evolution will proceed slowly enough to make direct observation of genetic difficult. For example, based on sequence variation at MHC loci in humans, Satta *et al*. (1994) determined that directly measuring allele frequency changes over time would not likely be possible if measurements occurred for less than 20 generations or with sample sizes of <5000 individuals. Similarily, model results that lead to the long lived polymorphism hypothesized for the *Rpm1* locus in *Arabidopsis* (see above) have relatively long period cycles with allele frequencies changing at a rate of about 1% per generation. It is not certain how general such results are, but these analyses of past selection do suggest that responses to selection will be difficult to observe directly (as with many traits under natural selection). This indeed seems to be the case, despite indications that parasites represent especially potent agents of natural selection (e.g. Bremermann, 1985).

Responses to selection. A response to selection has been frequently observed in agricultural systems. There are hundreds of examples from the parasite half of interactions, especially of agricultural pests evolving resistance to chemical pesticides (e.g. Gould *et al*., 1997) or to overcome resistant crop cultivars (e.g. Maxwell & Jennings, 1983). With regard to hosts, resistance can be directly selected for in artificial breeding programmes (Morris *et al*., 2000), whereas studies of seminatural or manipulated populations have provided evidence for the evolution of increased resistance to disease (Fenner & Ratcliffe, 1965; Ibrahim & Barrett, 1991; McDonald *et al*., 1998), or that an infusion of genetic diversity into the host population can dramatically alter disease patterns (Lively *et al*., 1990; Zhu

et al., 2000). Studies of bacteria-phage laboratory microcosms (e.g. Lenski & Levin, 1985) have also shown the evolution of resistance in hosts.

On the whole, simplified systems (e.g. agricultural) may give the impression that rapid selective change is a common aspect of antagonistic interactions. However, studies that followed parasite-associated gene frequency changes in natural, unmanipulated populations often yielded results that are difficult to interpret or contrary to expectations based on patterns of genetic variation for resistance (Fuxa *et al*., 1988; Burdon & Jarosz, 1991; Parker, 1991; Burdon & Thompson, 1995; Henter & Via, 1995; Little & Ebert, 1999). Studies have shown patterns ranging from no directional selection despite the presence of genetic variation for resistance (Henter & Via, 1995; Little & Ebert, 2001) to considerable genetic change, but without any apparent adaptive value (Burdon & Thompson, 1995; Little & Ebert, 1999). Some notable examples are given in Fig. 1.

Direct evidence for frequency-dependent genetic change comes from agricultural systems [e.g. barley and the mildew *Erysiphe graminis* (Barret, 1988)], or from bacterial microcosms (Levin, 1988). The only time study which directly tested for frequency-dependent cycling of host genes in a natural population showed that recently common snail clones tend to be overinfected with a trematode (Dybdahl & Lively, 1998), as would be expected if parasites adapt to, and then select against, common genotypes. Overall, however, given the scarcity of long-term studies that tested for frequency-dependent dynamics in natural systems, and the inconclusive results of short-term studies of directional selection, it would appear that present appreciation of the dynamics of interactions is, at best, limited.

Many cases where genetic change could not be observed may well be explained by low parasite prevalence or virulence-change simply would not have been expected. For those cases where change was justifiably expected, but not observed, enhanced knowledge of constraints on selection will provide an important foundation for assessing responses to selection. Three types of constraint (broadly defined) may in particular be hindering genetic change in the wild. First, the response to selection may be difficult to detect where genetic variance is small relative to the background of environmental variance (Williams, 1992). Further, selection on additive genetic variance may not occur at all if environmental variance simultaneously affects both resistance and fitness through separate pathways (Price *et al*., 1988). As suggested, studies of genetic variation which can provide insight into variance components in the wild are needed. Secondly, the role of trade-offs (costs of resistance) in constraining evolutionary change also deserve further attention. It has been widely discussed, although not often demonstrated, that resistance to parasites might be costly and traded off against other fitness components (reviewed in Coustau *et al*., 2000), and the existence of costs may critically determine whether interactions lead to the maintenance of polymorphism (May & Anderson, 1983). Thirdly, gene flow may hinder adaptive change if genes from either neighbouring populations or, for taxa with diapausing stages, from 'seed banks', contribute significantly to the genetic composition of the population. The importance of migration and spatial structuring for parasite–host coevolution has been reviewed by Burdon & Thrall (1999), and for many systems natural patterns may only make sense in a metapopulation context.

For observing longer-term dynamics, cases where neutral markers (e.g. allozymes, which can be used to assay large samples) may be linked to resistance loci have so far offered the best possibilities for tracking of gene frequencies (Dybdahl & Lively, 1998). Ultimately, where single genes of large effect are involved, it may be necessary to develop markers for these genes and track their frequencies directly. For example, it should be possible to develop polymerase chain reaction (PCR) primers from conserved regions of sequenced resistance genes and analyse variability in organisms amenable to evolutionary time-studies. The further development of quantitative trait loci (QTL) markers through crossing experiments is similarly promising. Data on resistance genes in invertebrates continues to accumulate (e.g. Aspán *et al*., 1995), and these hold special promise for evolutionary studies because many invertebrates have well understood ecological attributes, can be processed in large numbers, and have the short generation time required for temporal analyses of natural populations. Such studies would also have the prospect of gaining unprecedented insight into the nature of pathogen-imposed selection on host genomes. Combining realtime field measurements of the strength of parasite-imposed natural selection with data on molecular evolution might allow the signature of pathogen-driven selection in sequence data to be determined directly.

Summary and conclusions

Assessing the relevance of parasitism for evolutionary issues requires evidence for parasite-mediated selection. Four patterns ought to be evident: (1) parasitism reduces host fitness, (2) genotypes differ in susceptibility, (3) genotype frequencies change according to (2), and (4) in the longer term dynamics should encompass frequency-dependent allele frequency fluctuations. Patterns 1 and 2 indicate the potential for selection, and have been abundantly demonstrated, although details on the nature of the genetic control of resistance, and the occurrence of genetic interactions between host and parasite genes remain scarce for many taxa, especially arthropods. Pattern 3 has proven difficult to demonstrate directly. It would seem that the potential for selection is widely uncoupled from the response to selection. Indeed, there are relatively few examples of directly observed gene

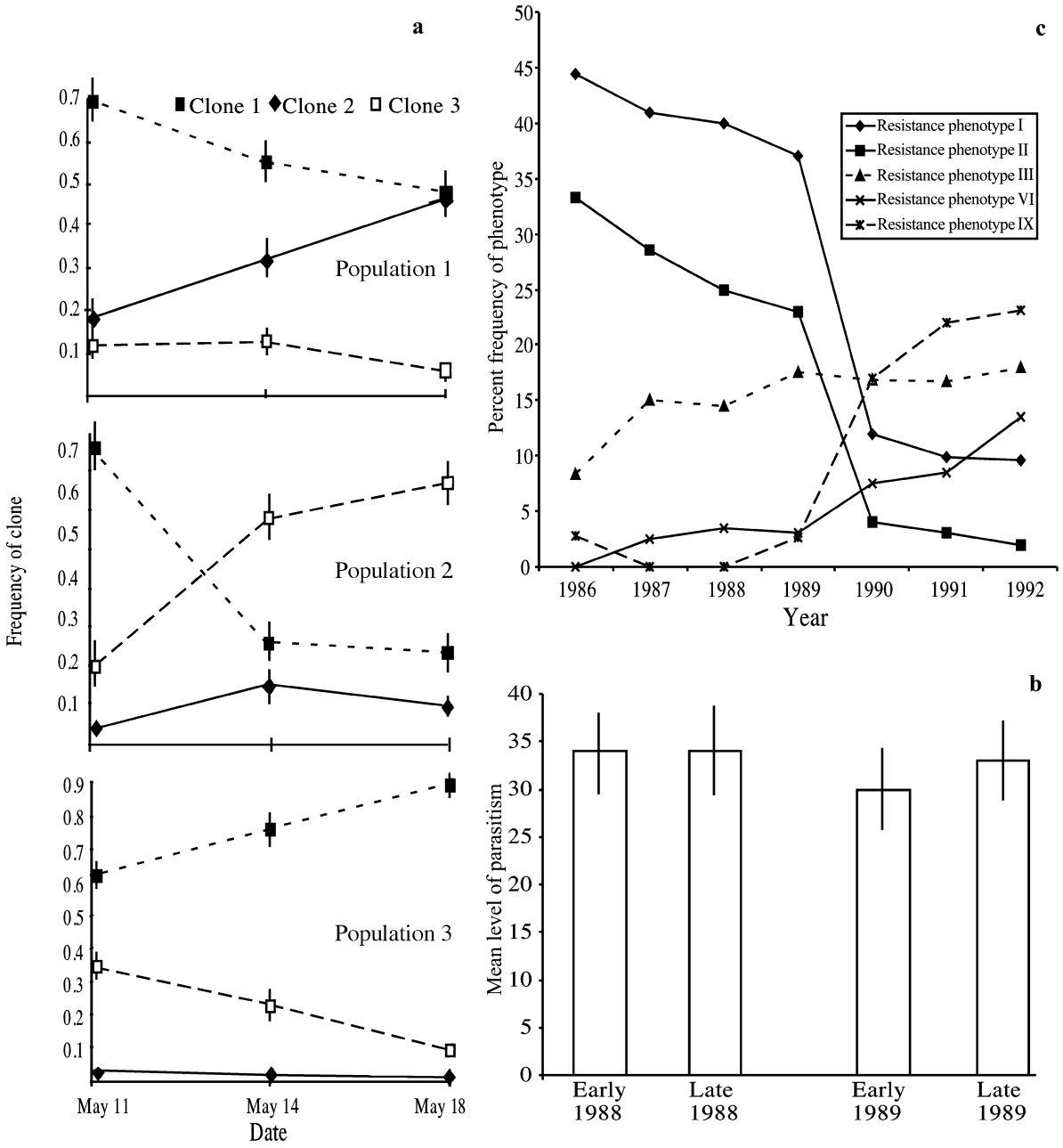

Fig. 1 Some examples of temporal studies of parasitism which observed either changes that would not have been expected based on patterns of genetic variation for resistance (a and b), or no dynamics at all (c) despite reasonable expectation of change. (a) Changes in the clonal frequency of three Daphnia clones from three separate but nearby ponds. In ponds 1 and 2 the comparatively susceptible clone 1 declined in frequency as expected, but in pond 3 it rose in frequency. Data from Little & Ebert (1999). (B) Results of a 5-year study of dynamics of host genotypes (the plant *Linum marginale*) in relation to susceptibility to the fungal pathogen (*Melampsora lini*). Phenotypes 1 and 2 were the most resistant, but still showed a marked decline, especially in 1989 when a major pathogen epidemic occurred. Data from Burdon & Thompson (1995). (c) The mean level of parasitism (caused by attack by a parasitoid wasp) did not differ between aphids collected early and late in the season in each of 2 years. Clonal variation for susceptibility to parasitoids was observed and parasitoids were a constant feature of the environment. Data from Henter & Via (1995).

frequency changes attributable to (nonanthropogenic) natural selection in the wild indicating that heritability data provide only a crude estimate of the net selection on any fitness-related trait (Williams, 1992; Ellner *et al*., 1999). Eloquent examples of responses to selection, such as that observed in the Galapagos finches studied by Grant and colleagues (Grant & Weiner, 1999) are celebrated in part because of their uniqueness. Finally, it would appear that we are far from a sufficient demonstration of pattern 4.

Are direct observations of parasite-driven dynamics rare because dynamics are not common, or is it a matter of detection? There is not an abundance of studies which have directly tested for gene frequency changes, but the studies we do have tended to give discouraging results. Parasite-driven dynamics may well be common, but too slow to detect, as indicated by analyses of past selection on disease resistance loci (Satta *et al*., 1994). However, for some theories, it can be argued that if dynamics are sufficiently common and powerful enough to generate the evolutionary phenomena attributed to them, then rapid fluctuations in host gene frequencies should be common and observable – both in the field and in real time. In particular, theoretical results which support the notion that coevolutionary interactions can select for sexual reproduction (the Red Queen hypothesis) indicate that the key mechanism is fluctuating epistasis, during which the sign of linkage disequilibria between alleles at different loci must switch within 3–4 generations (Peters & Lively, 1999). In other words, multilocus genotypes favoured today are disfavoured within a few generations (see also May & Anderson, 1983; Howard & Lively, 1994). Such rapid evolution of resistance genotypes does not appear to be a common feature of natural populations and further testing is required to determine whether parasitism is the potent evolutionary force many *in silico* experiments have indicated.

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