Plant-Parasite Coevolution: Bridging the Gap between Genetics and Ecology

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Annu. Rev. Phytopathol. 2011. 49:345–67

The *Annual Review of Phytopathology* is online at phyto.annualreviews.org

This article's doi: 10.1146/annurev-phyto-072910-095301

0066-4286/11/0908/0345$20.00

Keywords

resistance, avirulence, effector, frequency-dependent selection, polymorphism, boom-and-bust cycle

Abstract

We review current ideas about coevolution of plants and parasites, particularly processes that generate genetic diversity. Frequencies of host resistance and parasite virulence alleles that interact in gene-for-gene (GFG) relationships coevolve in the familiar boom-and-bust cycle, in which resistance is selected when virulence is rare, and virulence is selected when resistance is common. The cycle can result in stable polymorphism when diverse ecological and epidemiological factors cause negative direct frequency-dependent selection (ndFDS) on host resistance, parasite virulence, or both, such that the benefit of a trait to fitness declines as its frequency increases. Polymorphism can also be stabilized by overdominance, when heterozygous hosts have greater resistance than homozygotes to diverse pathogens. Genetic diversity can also persist in the form of statistical polymorphism, sustained by random processes acting on gene frequencies and population size. Stable polymorphism allows alleles to be long-lived and genetic variation to be detectable in natural populations. In agriculture, many of the factors promoting stability in host-parasite interactions have been lost, leading to arms races of host defenses and parasite effectors.

INTRODUCTION

Disease is possibly the most significant agent of natural selection. In both nature and agriculture, parasites limit plant growth, alter development, and reduce seed production. There is selection pressure on plants for resistance to parasites and equally on parasites to overcome host defenses. This confrontation drives coevolution, in which gene frequencies in one species determine the fitness of genotypes of the other species, and leads to diversity in host defenses and parasite weaponry. As with other areas of evolutionary biology, the need to understand numerous processes that affect disease at the level of populations means that theoretical research has had a central role in understanding coevolution.

Here, we review current ideas about coevolution of plants and parasites, particularly processes that generate genetic diversity. Three main themes emerge from recent literature. First, a wide variety of ecological and epidemiological factors can maintain genetic diversity in resistance and virulence. Many theoretical models involve complex sets of these factors, but it is not complexity as such that promotes diversity; rather, each individual factor is capable of maintaining diversity. Second, stochastic processes in population numbers and gene frequencies can prolong the lifetime of host and parasite alleles, sometimes greatly. Third, new methods offer the opportunity to test the plethora of factors studied in the theoretical literature. The design of experiments to test the models will be challenging, however, partly because disentangling the effects of numerous, sometimes-related factors is inherently difficult and partly because the experimental units must be whole populations of plants and parasites, not individual organisms. Current theory, however, offers a sound basis for further research on plant-parasite coevolution, especially on multiple resistance and virulence genes.

We focus on the gene-for-gene (GFG) interaction between plant resistance and pathogen avirulence (55, 125). This is by no means the only form of interaction between parasites and their host plants and rarely provides durable disease control in agriculture (17, 54), but it has been widely used as a model to understand the population genetic processes driving coevolution for three reasons. First, it describes clear differences between phenotypes in both the host and the parasite, which lend themselves to mathematical modeling and analysis. Second, by virtue of its clear phenotypes and generally simple genetics, the GFG relationship is a vigorous, rapidly advancing area of research and discoveries about it have been incorporated into coevolutionary models. Third, the general principles that emerge from the GFG system are widely applicable to other types of plant-parasite interaction and indeed to other kinds of victim-exploiter interaction.

Coevolution: a process in which two species, e.g., host and parasite, influence the evolution of one another

GFG: gene-for-gene

Avirulence: a parasite character that when recognized by a plant elicits host defenses

***RES*:** resistance in host

***res*:** susceptibility in host

***AVR*:** avirulence in parasite

***avr*:** virulence in parasite

Effector: a parasite molecule that modulates plant defense and development to the benefit of the parasite

THE BASIC GENE-FOR-GENE MODEL

In the simple GFG model, a plant has one locus with two alleles for resistance (*RES*) and susceptibility (*res*), and the pathogen has a corresponding locus with two alleles for avirulence (*AVR*) and virulence (*avr*). Several *AVR* genes encode effectors, which increase the ability of a pathogen to parasitize its host, for example by suppressing host defense (33, 48). There are four interactions in the well-known quadratic check (37) for GFG interactions describing effector-triggered immunity of plants to parasites (55). If an AVR parasite attacks a RES plant, the interaction is incompatible because the plant defends itself successfully. In the other three cases, the interaction is compatible and the parasite causes disease because either an *avr* pathogen is not recognized by the host or a *res* plant does not recognize the pathogen. More complex models include multiple pairs of plant *RES* and parasite *AVR* genes (39, 99, 101, 102, 107, 119, 126). In addition, many papers, especially in the zoological literature, use a model that has been described as a GFG interaction but would in fact be better described as an allele-for-allele model (19, 42). This type of model assumes one locus in the host with a series of alleles that interact with a corresponding series of alleles at one locus in the pathogen; each host

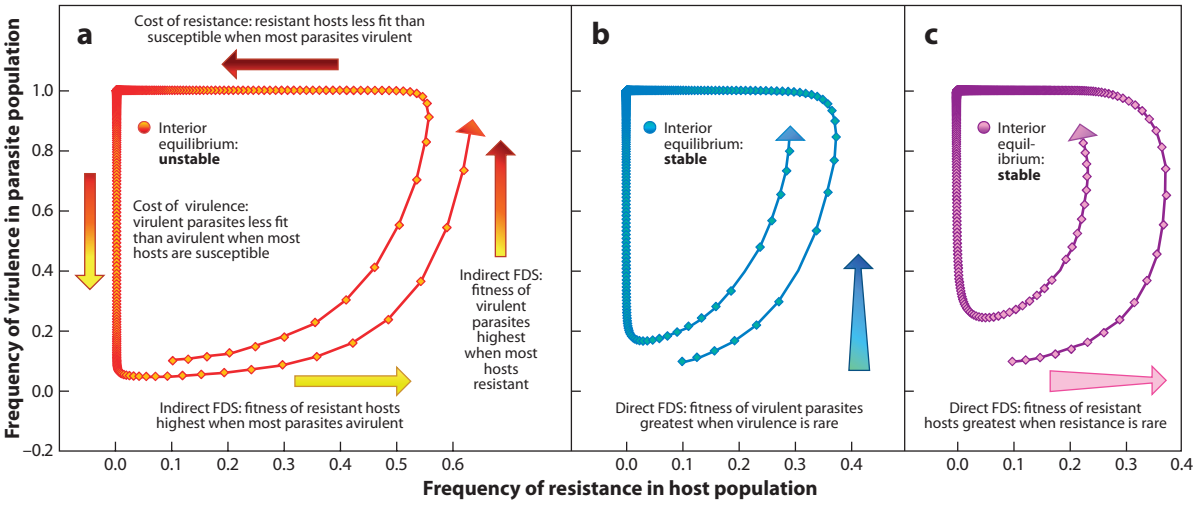

Figure 1

Cycles of frequencies of host resistance and parasite virulence. (*a*) An unstable cycle in a simple model of coevolution in a gene-for-gene system. Parameters: cost of virulence = cost of resistance = 0.05; cost to plant of being diseased = 0.3; cost to avirulent parasite of attacking a resistant host = 1.0. (*b*) A cycle stabilized by negative direct frequency-dependent selection (ndFDS) in the parasite generated by polycyclic infection. Cost to plant of being diseased by one generation of the pathogen = 0.11 and by two pathogen generations = 0.3 (120); other costs as in *a*. (*c*) A cycle stabilized by ndFDS in the host, generated by a seed bank in the soil (122). Selection coefficients as in *a*; fractional contribution of the seed bank to the next generation of the seed bank = 0.9; contribution of the seed bank to the next above-ground generation = 0.1.

resistance allele confers resistance to pathogens with the matching avirulence allele. Evidence for the existence of the allele-for-allele model are scarce (but see Reference 78), whereas GFG relationships are pervasive throughout the plant kingdom and have recently been discovered in invertebrates (142).

In theoretical models, the frequencies of resistance and virulence alleles in a population progress in a cycle, sometimes called the boom-and-bust cycle because of the often dramatic rise and fall in the effectiveness of resistance genes against pathogen populations in agriculture. In some models, such as spatially-extended populations in which each plant has a defined position in space (29, 102, 126), the cyclical dynamics may not be obvious when gene frequencies are averaged over the entire population, even though allele cycles occur in local subpopulations. The course of the cycle has four stages (**Figure 1*a***): (*a*) selection of host resistance when parasite virulence is rare; (*b*) selection of virulence by host resistance; (*c*) decline of the frequency of resistance when virulence is so common that resistance no longer confers an advantage; and (*d*) decline of the frequency of virulence when resistance is rare. In the latter two phases, resistance declines because it has a cost that outweighs its benefit when most parasites are virulent and thus pathogenic on resistant plants (131), and virulence then declines because it incurs a cost that exceeds its benefit to the parasite when most plants are susceptible to both virulent and avirulent pathogens (127). In most cases, these costs are described explicitly as parameters of the model (12, 14, 71, 137). In a few models, however, there are no explicit fitness costs in either or both species (29, 99, 126).

In general, there are a total of four costs in models of GFG coevolution. In addition to the fitness costs of resistance and virulence, they include the cost to the plant of being diseased and the cost to an *AVR* parasite of attacking an *RES* plant. The cost of being diseased must be greater than the cost of *RES*; otherwise, there

would be no net benefit to a plant in being resistant, and susceptibility (*res*) would become fixed in the plant population, followed by fixation of virulence (*avr*) in the parasite. The cost to a parasite of being unable to reproduce on a host to which it is avirulent is usually very high; in many cases, mathematical models are simplified by assuming that *AVR* parasites cannot reproduce on *RES* hosts at all.

Polymorphism: genetic variation within a species such that each allele's frequency is too high to be maintained by mutation alone

Balancing selection: natural selection that maintains two or more alleles of a gene at frequencies higher than that produced by mutation alone

Frequency-dependent selection (FDS): natural selection in which an allele's effect on fitness depends on its own frequency or that of other alleles

STABILITY AND INSTABILITY

The graph of frequencies of *RES* and *avr* genes spirals around an equilibrium point, a set of allele frequencies that remain constant under the combined effects of the four selection pressures. In addition to this interior equilibrium, there are also trivial equilibrium points where one allele each is fixed in the host and parasite populations. The interior equilibrium, where there is balanced polymorphism at both the *RES* locus in the host and the *AVR* locus in the parasite, may be stable or unstable. When it is unstable, the graph of gene frequencies spirals outward from the interior equilibrium until it reaches one of the trivial equilibria and alleles are fixed (**Figure 1*a***). When it is stable, it spirals inward, closer and closer to the interior equilibrium, where there is long-term persistence of genetic variation (**Figure 1*b*,*c***) (71, 72, 120).

The conditions that cause the interior equilibrium to be stable or unstable provide a deep insight into the evolution of host-parasite interactions, polymorphism in natural populations, and the design of experiments to test hypotheses about coevolution. In the stable situation, it is predicted that balanced polymorphism in relevant genes in both species is persistent, alleles of these genes are long-lived, and genetic variation is readily detectable in natural populations (12, 52, 113). In the unstable case, polymorphism is transient as successive host *RES* alleles appear, increase, and are overcome through loss of the corresponding *AVR* alleles in the parasite; alleles are short-lived, and *res* and *avr* alleles are generally fixed in host and parasite populations, respectively (12, 52). The hostile nature of host-parasite interactions has attracted militaristic metaphors. The stable case with balanced polymorphism has been described as trench warfare, as allele frequencies advance and retreat but change little over time (113, 143). The unstable case with repeated fixation of alleles has been called an arms race, as the two species acquire new weapons and defenses (52, 143). Over evolutionary periods of hundreds to thousands of years or even longer, these two scenarios are predicted to leave distinctive signatures on the level of genetic diversity and linkage disequilibrium at *RES* (100) and *AVR* (1) loci.

There is evidence for both patterns of polymorphism in plants and their parasites in nature and in agriculture. In natural populations, there is substantial variation at *RES* and *AVR* loci over short time scales (23, 64, 128, 129), and long-term balancing selection has been demonstrated by molecular data at *RES* genes in several species (see examples in References 97, 100), including *Arabidopsis thaliana* (3, 8, 113), the wild tomato species *Solanum pimpinellifolium* (24) and *Solanum peruvianum* (95), and the common bean, *Phaseolus vulgaris* (30). There are few examples of arms races at *RES* genes in natural populations (8, 13).

At parasite *AVR* loci, there is some evidence for both long-term balancing selection (5, 11) and arms races (11, 135; reviewed in 1, 116). There is accumulating evidence that over the comparatively short time of the few thousand years in which agriculture has been practiced, large numbers of *AVR* genes have proliferated in parasite genomes, then mutated to become ineffective (98). It is reasonable to predict that the corresponding host *RES* genes may have undergone a similar pattern of evolution, diversification (77, 106), selection, and then mutation to ineffectiveness; however, data are as yet lacking (115).

DIRECT FREQUENCY-DEPENDENT SELECTION

In population genetics, there are essentially two ways in which a balanced polymorphism can be generated. One is frequency-dependent selection (FDS), in which the strength of

natural selection is a function of gene frequencies. The other is overdominance, in which heterozygotes have higher fitness than either homozygote (76). The great majority of theoretical research on host-parasite coevolution relates to FDS; either the models have explicitly analyzed FDS or they can be interpreted in terms of FDS (see below). Although some early work investigated overdominance (82, 92), this important topic has mostly been neglected until fairly recently (146).

Two types of FDS operate in coevolving hosts and parasites. They describe quite different processes and have different effects on coevolution. In one case, the frequencies of host alleles modify natural selection on the parasite and vice versa. Specifically, a low frequency of *avr* increases the fitness of *RES* hosts (the bottom part of the boom-and-bust cycle; **Figure 1*a***) and an increasing frequency of *RES* hosts increases the fitness of *avr* parasites (right-hand part of **Figure 1*a***). This has been termed indirect FDS (iFDS) because gene frequencies in one species affect the fitness of the other species (120). Many papers have used the term FDS without qualification to describe iFDS in the context of disease; this usage appears to have a long history in population genetics (28, 38, 50, 51). iFDS acts together with the costs of resistance and virulence (top and left of **Figure 1*a***) to drive the cyclical dynamics of the model (38).

The term FDS is used more often in population genetics to describe a process quite different from iFDS in which an allele's frequency affects its own contribution to fitness (27). This is called direct FDS (dFDS), in contrast to iFDS (120). The role of dFDS in host-parasite coevolution has been analyzed in hosts and parasites that are either haploid or reproduce by selfing, which, in evolutionary terms, amount to much the same thing, as in both cases each individual has one allele of each gene, barring rare mutations. To maintain polymorphism in both the *RES* locus in the host and the *AVR* locus in the parasite, dFDS with a negative sign (ndFDS) must act on either or both loci, such that an allele makes a decreasing contribution to fitness as its frequency rises and at some point its net effect on fitness is zero (see sidebar, A Condition for Stable, Balanced Polymorphism in Host Resistance and Parasite Virulence). The processes that generate dFDS also apply to out-crossing diploids, where overdominance may also play a part.

The effects of the two forms of FDS are distinct. iFDS is inherent in the host-parasite interaction and drives the cyclical dynamics of the boom-and-bust model (**Figure 1*a***). ndFDS, by contrast, stabilizes polymorphism in *RES* and *AVR* genes at the interior equilibrium point (**Figure 1*b*,*c***). In the absence of ndFDS, the interior equilibrium is unstable and the graph of *RES* and *avr* gene frequencies spirals outwards to fixation at one of the trivial equilibria.

A CONDITION FOR STABLE, BALANCED POLYMORPHISM IN HOST RESISTANCE AND PARASITE VIRULENCE

Negative direct frequency-dependent selection (ndFDS) stabilizes balanced polymorphism in host resistance and parasite avirulence (120). Consider natural selection acting on a locus with two alleles in a haploid species. Individuals with allele **G** have lower mean fitness than **g** individuals, in the ratio of $1{:}1-\sigma$ ($0 \leq \sigma \leq 1$). The allele frequencies are G and g ($G + g = 1$). When natural selection is constant, the logit function of allele frequencies, $\log(G/g) = \gamma$, increases by $\log(\sigma)$ each generation.

When there is dFDS, however, the change in γ ($\Delta\gamma$) depends on the alleles' frequencies. If there is a value of G (G_{eq}: $0 < G_{eq} < 1$) that does not change under natural selection and if G is restored to G_{eq} if it deviates in either direction, then G_{eq} is a stable equilibrium, and both alleles are maintained in the population. Hence, dFDS is negative (i.e., there is ndFDS) because natural selection for **G** declines as its frequency rises. Mathematically, we require $d\Delta\gamma/d\gamma < 0$ around $G = G_{eq}$.

A system of two species is more complex. If the host has alleles **R** and **r** for resistance and susceptibility, the parasite alleles are **A** and **a** for avirulence and virulence [$\rho = \log(R/r)$ and $\alpha = \log(A/a)$]. The relationship $d\Delta\rho/d\rho + d\Delta\alpha/d\alpha < 0$ causes the graph of R and a to spiral inwards towards equilibrium at (R_{eq}, a_{eq}). Hence, stable polymorphism at *RES* and *AVR* loci can arise when ndFDS acts on either resistance or virulence or both.

Indirect frequency-dependent selection (iFDS): FDS in which the fitness effect of an allele in one species depends on an allele frequency in another species

Direct frequency-dependent selection (dFDS): FDS in which the effect of an allele on fitness depends on its own frequency

Negative direct frequency-dependent selection (ndFDS): dFDS in which the contribution of an allele to fitness declines as its frequency increases

Deme: a local panmictic population, often with a characteristic gene pool; a component of a metapopulation

PROCESSES MAINTAINING POLYMORPHISM IN COEVOLUTIONARY MODELS

dFDS is a process that operates at the population level, not on individual organisms, because the fitness of an individual depends on gene frequencies in the population as a whole. In host-parasite coevolution, all processes that generate ndFDS in theoretical models involve uncoupling of cycles of gene frequencies in time or space. In the simple boom-and-bust cycle (**Figure 1*a***), by contrast, the dynamics of host and parasite gene frequencies in a single population are completely coupled and there is no dFDS. Partial uncoupling of host and parasite life cycles in time in a single population implies that the dynamics of *RES* and *AVR* gene frequencies are not fully synchronized (119, 120, 122). Uncoupling of boom-and-bust cycles in space occurs if different demes linked by migration exhibit different frequencies of coevolutionary oscillations. This effect might also generate sufficient ndFDS to maintain balanced polymorphism.

The seminal model of GFG coevolution (70, 71) assumes that both host and parasite are haploid, each in a single population. Host and parasite generations are discrete and nonoverlapping and the species reproduce synchronously. Host and parasite individuals meet randomly at rates depending on their relative frequencies, as defined by frequency-dependent disease transmission (4). In such a case, allele dynamics are unstable (**Figure 1*a***), leading eventually to fixation of host and parasite alleles and thus to arms races when several pairs of *RES* and *AVR* genes are involved (36, 105).

This basic model has since been developed, with the aim of finding conditions that generate long-term polymorphism in both hosts and parasites. Although theoreticians from several disciplines, including ecology, epidemiology, and pathology, have contributed to a research effort lasting over 40 years, the conditions that lead to balanced polymorphism ultimately relate to population genetics. We show here that the factors that have been shown by diverse theoretical approaches to promote stable or quasi-stable polymorphism fall into one of two categories: (*a*) those that lead to stable polymorphism by generating ndFDS at *RES* or *AVR* loci or both or, in one case, by overdominance (**Table 1**) and (*b*) those that promote statistical polymorphism, an increase in the time to allele fixation

Table 1 Factors predicted to promote balanced polymorphism in coevolving hosts and parasites by uncoupling host and parasite life cycles in time or space and thus generating negative direct FDS (ndFDS)

Cause of uncoupling of host and parasite life cycles	Factor in models that leads to ndFDS	References
Asynchrony in time between host and parasite life cycles	Polycyclic disease with autoinfection but also some alloinfection	(119, 120, 126)
	Overlapping host generations: seed banks in soil or perenniality	(29, 122)
	Overlapping parasite generations: durable parasite reproductive structures	None
	One-generation asynchrony between host and parasite life cycles	(62, 71–74)
Asynchrony in space between host and parasite life cycles (in a heterogeneous environment)	Spatial variation in disease severity	(29, 45, 88)
	Spatial variation in costs of resistance and virulence	None
Genetic factors (single or multilocus gene-for-gene interactions)	Mutation in host and parasites	(62, 99, 101, 102, 107, 108)
	Diploid species with overdominance	(146)
Epidemiological feedback	Density-dependent disease transmission	(39, 44, 53, 61, 122, 126)

Table 2 Models in which statistical polymorphism is promoted in coevolving hosts and parasites by lengthening the time to fixation of alleles or promoting random genetic drift

Class of factor favoring polymorphism	Specific factors included in models	References
Genetic factors	Multilocus gene-for-gene (GFG) interactions without costs of resistance or virulence	(99, 126)
	Multilocus GFG interactions with multiplicative costs	(39, 60, 99, 101, 102, 107, 108, 119)
	Multilocus GFG interactions with epistatic interactions among loci for costs	(119)
	Multiple alleles at a single locus	(108)
	Genetic drift in finite populations	(62, 99, 126)
Ecological factors	Spatial structure of host and parasite populations: homogeneous environment, polymorphism in each deme	(29, 39, 62, 126)
	Spatial structure: polymorphism sustained by pacemaker demes out of synchrony with rest of metapopulation	(45, 102)
	Random variation of disease severity in time	(60)

reflected in polymorphism that may be persistent but is ultimately transient (2) (**Table 2**).

Factors Generating Direct Frequency-Dependent Selection

Stabilization of allele cycles by dFDS is due to the uncoupling of host and parasite life cycles in time or space (**Table 1**). Uncoupling in time can occur, for example, when a parasite has a polycyclic life cycle, that is, more than one generation per host generation (119, 120, 126). The effect is strongest when there is a high rate of autoinfection, that is, when plants tend to be reinfected by parasites produced on those same plants (9), but there is also some alloinfection, that is, some parasite propagules cause disease on plants that were previously uninfected. The high frequency of autoinfection generates ndFDS by decreasing selection for *avr* parasites when the frequency of *avr* is high (**Figure 2**; 120). In another example, life cycles can also be uncoupled within a growing season when a parasite completes its life cycle before its host plant does; this results in delayed genetic feedback between host and parasite populations. Such a delay causes changes in allele frequencies resulting from natural selection to occur sequentially in host and pathogen populations, uncoupling the dynamics of allele cycles in the two species and thus promoting stable equilibrium (36, 71, 72, 105).

Life cycles may also be uncoupled when the time scales of host and parasite generations differ over a period of years. Overlapping plant generations promote dFDS through the storage of genetic diversity; in plants this occurs in seed banks in the soil, such that dormant seeds survive several years before germinating (29, 122) or in perennial species (122). A long-lived seed bank has allele frequencies close to the long-term mean. When the frequency of any gene, *RES* included, in the current standing population of plants differs from the long-term mean, the contribution of the seed bank tends to draw the gene frequency closer to the long-term mean. As *RES* genes tend to have low long-term mean frequencies, approximately the same as the cost of virulence (see below), the seed bank has a stronger effect in reducing the frequency of *RES* when that frequency is high. This generates ndFDS on *RES* genes (122). Storage of genetic diversity in the parasite has not yet been investigated in detail but overlapping of parasite generations can occur through long-term survival of reproductive structures. Perennating sexual structures such as cleistothecia or chasmothecia in some fungi and eggs of nematodes

Polycyclic: describes a disease in which there are several parasite generations during the lifetime of a host plant

Autoinfection: an infection of a plant caused by a parasite propagule produced on the same individual

Alloinfection: an infection of a plant caused by a parasite propagule produced on a different individual

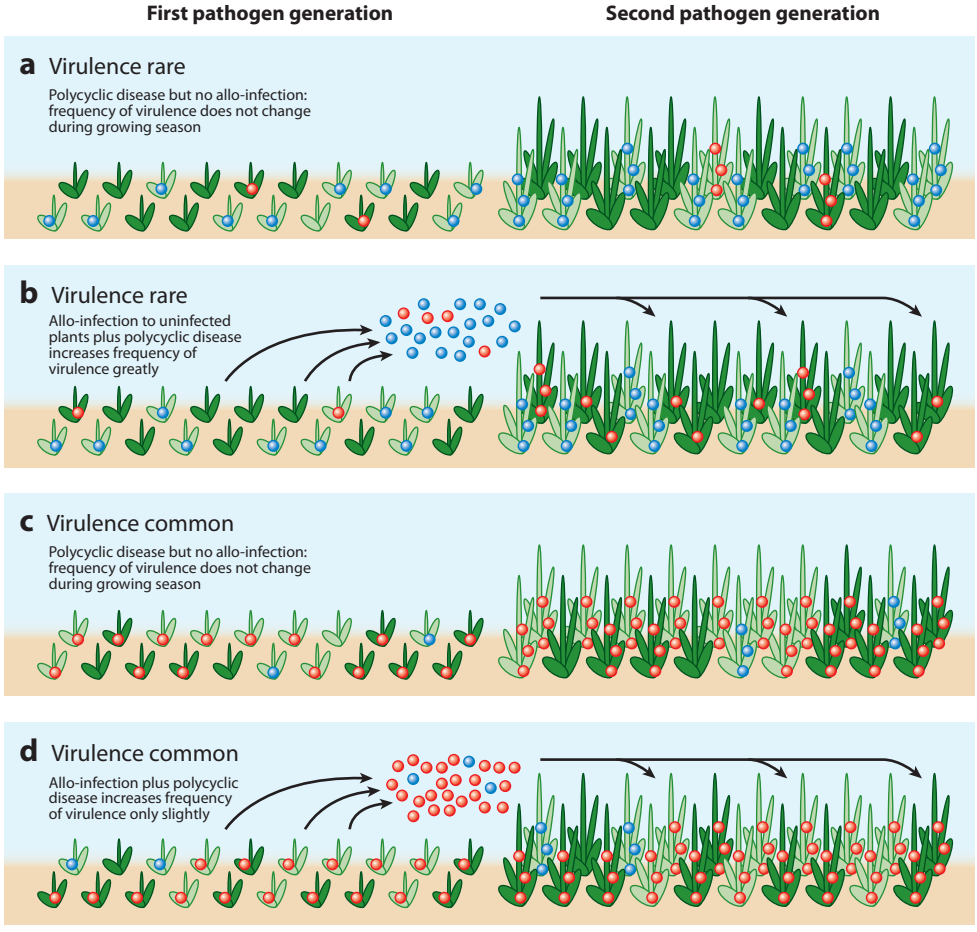

Figure 2

Negative direct frequency-dependent selection (ndFDS) acting on the parasite's avirulence gene, generated by polycyclic infection combined with a high frequency of autoinfection (120). Colors: dark green plants, resistant; light green plants, susceptible; red spheres, virulent parasites; blue spheres, avirulent parasites. Avirulent parasites cannot infect resistant plants. When there is no parasite dispersal (*a* and *c*), the frequency of virulence is not altered by a second generation of parasite reproduction. When the frequency of virulence is low (*a* and *b*), virulent parasites gain substantial additional fitness by dispersal to undiseased, resistant plants. When the frequency of virulence is high (*c* and *d*), the benefit of dispersal in the second generation is small. Hence, the contribution of virulence to parasite fitness is greatest when it is rare (compare *b* with *d*).

can survive in the soil for several years before initiating new infections.

Host and parasite generations can be separated in space as well as time. There are two aspects to spatial variation. First, environmental conditions may not be homogeneous, so selection pressures may vary from place to place. Second, spatial separation may restrict gene flow between demes by reducing dispersal of seeds and spores. A spatially heterogeneous environment—for example, for disease severity—can promote asynchrony in host-parasite coevolution (29, 45, 88). dFDS is generated by the migration between two or more demes that exhibit asynchronous coevolutionary cycles, in accordance with models of

migration-selection balance in which demes have different environmental characteristics (57, 75).

Epidemiological models with density-dependent disease transmission create dFDS. When transmission of a parasite genotype depends on both its own frequency and also the density of suitable hosts, the strength of selection for that genotype is reduced when it is common (39, 44, 53, 61, 122, 126). Density-dependent disease transmission is assumed to describe life cycles of parasites following the off-season (e.g., overwintering or oversummering), when the inoculum load at the start of the next host season determines the severity of the epidemic (44, 46, 53). The robustness of estimates of parameters that describe epidemics over thousands of generations, however, is open to question because the intensity of botanical epidemics is determined at least as much by environmental conditions as by the quantity of inoculum that initiates epidemics (26).

Mutations in *RES* and *AVR* genes also promote dFDS, although this effect is weaker than many of the ecological and epidemiological processes discussed. A mathematical description is that mutation creates a limit cycle (79), which attracts allele frequencies close to the boundaries (62). In biological terms, high mutation rates prevent alleles from going extinct (62, 99, 101, 102, 107, 108) and promote diversity at loci that might not be under selection in the current population (99).

Factors Generating Statistical Polymorphism

Even when the environment is homogeneous, the cycles of host and parasite allele frequences in different demes may be out of synchrony even if they are connected by gene flow. In such a situation, each population receives immigrant seeds or pathogen propagules, such as spores, that have genotype frequencies determined by the history of natural selection in their source population, not in the target population in which they have arrived. Gene flow between populations that are not synchronized links the allele cycles in these locations, resulting in polymorphism that may be long-lived even though it is not permanent. This effect is most striking for multiple *RES* and *AVR* gene pairs (102, 126). Two classes of factor promote this long-lived but ultimately transient statistical polymorphism but do not generate dFDS (**Table 2**).

The effect of spatial structuring of populations with a homogeneous environment is demonstrated by metapopulation models. High rates of extinction of local populations followed by recolonization of these demes produces large, random differences in allele frequencies between demes, sustaining transient polymorphism and increasing the lifetime of alleles (29, 39, 45, 62, 102, 126). Polymorphism can thus be maintained in each deme and in the metapopulation as a whole. Some metapopulation models also contain one or more factors identified as generating ndFDS (**Table 1**), which can convert transient, statistical polymorphism to permanent, balanced polymorphism (29, 39, 62, 126).

Numerous GFG models have considered multi-locus systems with two (62, 108) or more loci (39, 60, 99, 101, 102, 107, 119). Multi-locus GFG systems can display complex, sometimes chaotic changes in allele frequencies (60, 101, 107, 108). When mutation rates are low and the population size is finite, genotypes with many (or even all) virulent alleles may be fixed in the parasite population (107, 119), but in general, the existence of multiple loci slows the rate of allele fixation (62, 99, 119). The combination of multi-locus interactions and metapopulation structure promotes a very high level of random genetic drift and contributes to long-term statistical polymorphism.

Spatial models can generate complex patterns in the distribution of genotypes. In a metapopulation, a few demes can become desynchronized from the remainder and act as pacemakers, driving waves of allele frequencies to spread regularly over the whole metapopulation (45, 102). This occurs with several *RES* and *AVR* gene pairs, in a two-dimensional space

Metapopulation: a population of populations; a set of spatially distinct demes linked by gene flow of pollen or seeds

Random genetic drift: stochastic changes in gene frequencies due to random sampling of gametes between generations; most pronounced in small populations

with limited migration (a viscous metapopulation). Although intriguing, there is currently a lack of empirical data to test the hypotheses represented by these models.

Overdominance: a state in which a property of a heterozygote, such as fitness, exceeds that of either homozygote

Factors Impeding Stable Polymorphism

Although most elaborations of the basic GFG model (70) promote stable polymorphism, some do not. Induced resistance, the activation of plant defense through the salicylate-dependent or jasmonate-dependent pathways as a result of a challenge such as an *AVR* parasite attacking a *RES* plant (109, 139), increases the selective advantage of *RES* alleles in the population. This causes selection for resistance to depend less strongly on the frequency of the *RES* allele and destabilizes the interior polymorphic equilibrium (121). Fixed perturbations of an allele frequency such as those that occur in agriculture, also impede stability, for example, by forcing a constant increase of the frequency of *RES* in the plant population (117, 118).

Overdominance

Early models of coevolution emphasized the selective advantage of heterozygotes in maintaining balanced polymorphism (82, 92). Overdominance is a property of diploid organisms in which heterozygotes have higher mean fitness than either class of homozygote. In host-parasite interactions, overdominance arises when a host has two resistance alleles at a locus and is thus resistant to a greater proportion of the parasite population than either class of homozygote, with only one resistance allele at that locus. More recently, however, the great majority of research has considered ecological and epidemiological factors that generate ndFDS in haploid parasites and haploid or selfing hosts (**Table 1**). In diploid hosts, however, alleles can be masked from negative selection and thus prevented from becoming extinct. This means that polymorphic equilibria can exist and be stable, even when there is no cost to the parasite of virulence (146).

Complexity and Stability

Although many of the published models of host-parasite coevolution, including GFG coevolution, are complex, an important general conclusion is that it is not complexity as such that generates stability. With the exception of one recent paper on overdominance (146), one or more of the many factors in each of these complex models promotes ndFDS, stabilizing *RES* and *AVR* allele frequencies at intermediate values. In models that lack ndFDS, polymorphism is transient, even if it lasts a long time, and alleles are eventually fixed unless mutation rates are high.

COSTS OF RESISTANCE AND VIRULENCE

Costs of resistance and virulence do not stabilize polymorphism at *RES* and *AVR* loci. However, they, along with two other costs, the loss of plant fitness caused by disease and the high penalty to an *AVR* pathogen that fails to infect a *RES* plant, determine the frequencies of *RES* and *avr* in the host and parasite populations at equilibrium. There is an interesting reciprocal relationship between costs and gene frequencies. In a wide range of models, the frequency of *RES* at equilibrium is approximately equal to the cost of *avr* and the frequency of *AVR* is approximately proportional to the cost of *RES* (38, 71, 74, 120). This is the result of negative feedback in the host-parasite interaction, so the ultimate effect of increasing the cost of *avr* is to increase the frequency of *RES*, leaving the frequency of *avr* unchanged, while increasing the cost of *RES* reduces the frequency of *avr* (**Figure 3**; see also 20, 38).

The reciprocal relationship of gene frequencies in one species and costs in the other species leads to the prediction that functional *RES* alleles and *AVR* alleles are likely to be rare in host and pathogen populations, respectively, because the costs of *avr* to the pathogen and of *RES* to the host are generally small (7, 14, 83, 127, 138; see Reference 131 for an example of a costly *RES* gene). This is a robust prediction of

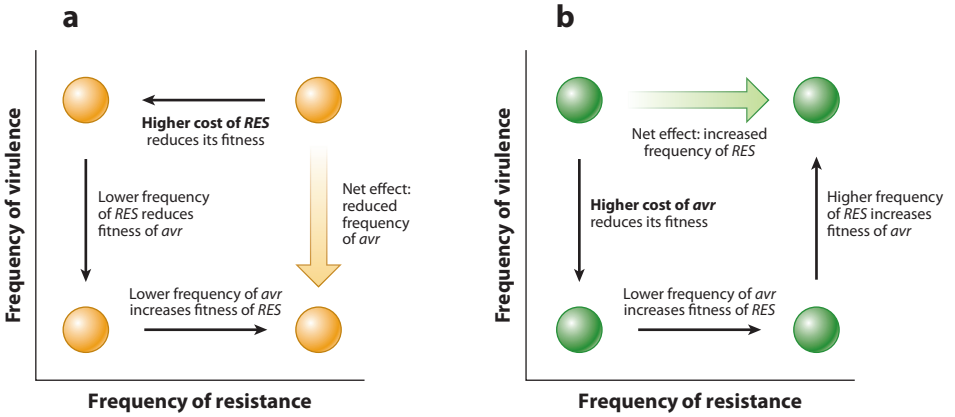

Figure 3

The reciprocal relationship between costs of resistance and equilibrium frequency of virulence and vice versa. (*a*) The net effect of increasing the cost of resistance is to reduce the equilibrium frequency of parasite virulence. (*b*) The net effect of increasing the cost of virulence is to increase the equilibrium frequency of host resistance.

many models of host-parasite coevolution (12, 38, 39, 119, 120, 122). Recently, several very large families of parasite effector genes have been discovered, including several with members which are also *AVR* genes (98, 103, 111), whereas plants have numerous families of *RES* genes (80, 81, 140, 145). Extrapolating from the prediction about frequencies of individual *RES* and *AVR* alleles, any individual plant genome is likely to contain few functional *RES* genes on average and any individual pathogen genome to have few functional *AVR* genes. As a corollary, one would predict that families of *RES* and *AVR* genes involved in GFG interactions should be large, but in any individual, most members of each family should be nonfunctional. This is the case for the *EKA* family of effector genes in *Blumeria graminis*, the barley powdery mildew fungus (98, 111).

The cyclical dynamics of *RES* and *avr* frequencies depend on fitness costs causing those alleles to be removed from the population once they no longer benefit the host or parasite. Costs of resistance in plant disease have been reviewed elsewhere (14, 18, 20). Several types of cost have been attributed to *RES* genes involved in GFG interactions. Over-expression of *Prf* in tomato enhanced levels of salicylic acid (SA) and led to constitutive expression of pathogenesis related (PR) genes (90), which suggests some *RES* genes might cause some loss of fitness when expressed at a normal level if production of SA and expression of PR genes incurs costs. Furthermore, some resistance genes, such as *Mla* genes in barley, are constitutively expressed at very low levels but are strongly induced upon infection by *B. graminis* (25), implying that high levels of expression in the absence of the pathogen might be harmful to the plant.

A prediction of a coevolutionary model with several *RES-AVR* gene pairs is that an equilibrium in which all interacting plant and parasite loci are polymorphic is more likely to be stable when the marginal cost of resistance decreases with each additional *RES* gene (119). This accords with current understanding of plant defense, as different genes for resistance to the same disease elicit largely overlapping sets of defenses (58, 132), but has not been tested rigorously. By contrast, hybrid necrosis, caused by an autoimmune reaction, may occur when plant genomes that have diverged in allopatry and contain different *RES* genes are brought together in one zygote through sex (15). In this case, the cost of resistance is greater when the plant contains more *RES* genes; that is, the cost

of having two *RES* genes that act together to cause hybrid necrosis is very much greater than the cost (if any) of having either gene separately. It can be predicted, therefore, that polymorphism in genes involved in hybrid necrosis is likely to be unstable.

It might be expected that virulence would be costly because several *AVR* genes have effector activity. However, experiments on costs of virulence have produced somewhat variable results, with some being high and easily detectable but many others appearing to lack a significant cost (116). A multi-locus model predicts that stability is most likely when costs of virulence increase as each additional AVR activity is lost (119). Again, this accords with current evidence, as some *AVR* genes are members of large families (98, 103, 111). Many *AVR* genes have effector activity (48, 87, 93), so if they partially complement one another, the loss of one *AVR* activity may incur little loss of fitness to the pathogen, whereas losing each additional *AVR* gene might incur an increasingly severe penalty. The hypothesis that fitness costs of virulence are synergistic accords with experimental data on *Xanthamonas axonopodis* pv. *vesicatoria* of *Arabidopsis thaliana* (141) and *Phytophthora infestans* (late blight of potato) (83). Recently, it was shown that costs of virulence vary between environments in *Puccinia striiformis* f. sp. *tritici* (yellow rust of wheat) (7) and in *P. infestans* (83). This is significant because variation in environmental conditions that leads to spatial variation in selection coefficients can lead to stable polymorphism (45, 88).

MODELS WITHOUT FITNESS COSTS

In some GFG models, polymorphism is maintained even though there are no explicit costs of *RES* and *avr* alleles (29, 99, 126). These models are intriguing because they challenge the view that costs that balance the benefits of *RES* and *avr* alleles are essential to maintain diversity. However, the actual process by which they maintain genetic diversity is not entirely clear because the complex stochastic processes involved have not been analyzed mathematically. Features that these models share are strong spatial structure with limited migration and high mutation rates in both species. In addition, two models have several pairs of *RES* and *AVR* loci (99, 126). One possibility is that the combination of high mutation rates with very high random genetic drift in small local subpopulations generates strong statistical polymorphism (see above). Strong iFDS allows *avr* alleles to achieve very high frequencies but not to invade the entire population or metapopulation (29, 99, 126) because random genetic drift allows minor genotypes to be maintained locally. This eases selection pressure on the plant and causes *RES* and *res* (susceptibility) alleles to be neutral with respect to natural selection. The probability of an allele becoming fixed by genetic drift is proportional to its frequency so both *RES* and *res* alleles can be maintained if migration is sufficiently limited. In summary, we suggest that this group of no-cost models maintains long-term polymorphism because mutation constantly generates genetic variation, short-range dispersal allows *avr* alleles to become locally fixed, and frequencies of *RES* and *res* alleles are subject to high levels of genetic drift in small, local populations, especially when the cost to plants of being diseased is small (29). In addition, mutation generates a weak form of ndFDS (62), which might help to stabilize gene frequencies.

STOCHASTIC CYCLING

Most models of GFG coevolution assume that the population sizes of plants and their parasites are infinite. This convenient assumption simplifies the analysis of what are often complex models. However, the existence of a finite number of individuals in a population gives rise to random genetic drift, and the resulting stochastic variation in population size and gene frequencies has a significant effect on the coevolutionary allele cycle. There are different processes in situations when the interior polymorphic equilibrium is stable or unstable. When it is stable, as in **Figure 1*b*,*c***, random

genetic drift and mutation constantly nudge allele frequencies away from the stable equilibrium point, then natural selection drives them back again (120). Allele frequencies therefore have quasi-stable values with stochastic cycles of *RES* and *avr* frequencies close to the polymorphic equilibrium, rather than stable, constant values. This is essentially the trench warfare process (113), with small advances and retreats in the parasite weaponry and host defenses.

In unstable models, host and parasite alleles can go extinct in finite populations because their frequencies are driven close to the boundaries (see **Figure 1*a***), and there is a finite probability that they may be eliminated (62, 72, 74). When mutation occurs at a high rate, however, it may prevent loss of alleles by constantly reintroducing genetic variation (29, 62, 99, 102, 126), giving rise to apparently cyclical dynamics: introduction of an allele by mutation, a series of boom-and-bust cycles, the stochastic loss of the allele, and then its reintroduction by a new mutation (62, 72, 74).

EVIDENCE FOR COEVOLUTIONARY HYPOTHESES

Theoretical research on host-parasite coevolution, including the GFG relationship, has generated many hypotheses for the generation of diversity in *RES* and *AVR* genes and for the stabilization or otherwise of polymorphism. Data from three types of studies, population genetics, ecological research, and controlled experiments, can be used to test these hypotheses. These tests are challenging, especially for hypotheses concerning stability, because dFDS and the factors that promote it operate over a population, not at the level of individual organisms. The experimental units therefore need to be whole populations rather than individuals. Likewise, the degree of overdominance, referring to the fitness advantage of heterozygotes at a *RES* locus in an out-crossing, diploid plant, depends on *AVR* allele frequencies in the parasite population.

Population Genetics

With the advent of high-throughput genome sequencing, the signatures of trench warfare (high genetic diversity and large numbers of DNA sequence variants at intermediate frequencies, causing high values of Tajima's D statistic) (113), and of arms races (low genetic variation and high linkage disequilibrium) (13) can be detected at known or new candidate *RES* and *AVR* loci sequenced for several host and parasite individuals in a population. This will allow ecological processes leading to the scenarios to be identified. Studies that combine population genetic analysis of balancing selection with phenotypic data from pathology experiments should indicate whether or not dFDS has driven coevolution at these genes (6, 86, 94, 95) and could form the starting point for experiments to test factors promoting dFDS.

Ecological Studies

The theory of the Geographic Mosaic of Coevolution, which describes spatially structured heterogeneous populations (123, 124), is widely applicable to plants and their parasites (67, 68). The theory is general and does not rely on specific assumptions about the genetic basis of the interaction. It assumes the presence of hot and cold spots of coevolution, where parasite numbers range from high to absent, respectively. Gene flow between demes with different selection coefficients can maintain polymorphism (57), so variation in the parasite load suffered by the host promotes the long-term maintenance of polymorphism in both species (45, 88). This ecological theory could be applied to construct tests for trench warfare or arms races using empirical field data (41) in local adaptation studies (43, 59, 89).

A compelling example of local adaptation in a heterogeneous environment is provided by *Plantago lanceolata*, an annual forb, and its powdery mildew parasite *Podosphaera plantaginis*. The severity and prevalence of disease vary between demes and season (65, 66, 110),

creating a mosaic of different local coevolutionary scenarios ranging from strong host-parasite interactions to demes where only the plant is present. Geographic structure and heterogeneous habitats are thought to promote dFDS and thus, stable polymorphism (68). A major problem with such ecological studies, however, is that either data are obtained over a short time scale, preventing the observation of dFDS, or too many factors influence the outcome of the coevolution and it is difficult to test rigorously which factors promote dFDS (but see Reference 31, where the egg bank in *Daphnia* has the same effect on coevolution as a seed bank) (122).

Experimental Coevolution

Ideally, experiments to investigate dFDS would examine the influence of factors thought to promote dFDS one at a time, measuring the fitness and frequencies of host and parasite genotypes over several generations in a controlled environment. A candidate for a suitable experimental system might be a bacterium-phage interaction (16, 84), where factors analogous to seed banks, polycyclic infection, or heterogeneous environments (16, 84) can be recreated in petri dishes. Similarly, some plants, such as *Arabidopsis thaliana*, are suitable for controlled infection experiments over a few generations because of their short generation time and the possibility of measuring seed and spore production of plants and parasites (63, 96, 131). An example of an appropriate experiment would be to measure changes in host and parasite gene frequencies over a few generations at a point where the allele cycle moves rapidly, particularly where the frequency of *RES* is high and that of *avr* is low (bottom-right of each panel in **Figure 1**). A factor that promotes stable polymorphism would be predicted to push the graph of *RES* and *avr* frequencies inwards, towards the interior, polymorphic equilibrium.

OTHER COMPONENTS OF PLANT DEFENSE

The principles used to model GFG coevolution can be expected to be applicable to other components of plant defense, although theoretical models may need to be adapted to the details of each particular system. Key features are the cyclical dynamics of host and parasite gene frequencies, the role of dFDS in stabilizing polymorphism, and the reciprocal relationship between fitness costs and equilibrium frequencies of resistance and virulence. The GFG theory may help to illuminate other long-term evolutionary processes, including the emergence of novel plant diseases (91) and speciation in plants and parasites (47). In addition to direct recognition of effectors (32), as in some GFG relationships, areas for future study could also include (*a*) the inverse GFG relationship, in which a fungus produces a host-selective toxin (35, 114), (*b*) indirect recognition of effectors by guard proteins (133, 134), such as the *Pto-Prf-AvrPto* or *RCR3-Cf2-Avr2* interactions in tomatoes (33, 55)—note that the principles of GFG coevolution apply equally to the evolution of the guard protein (*Prf*, *Cf2*) and of the target protein (*Pto*, *RCR3*)—and (*c*) basal resistance to pathogen-associated molecular patterns (PAMPs) encoded by pattern-recognition receptor genes (PRRs) (104, 147). In the last of these cases, it is striking that the extremely high predicted cost to the parasite of losing or modifying a PAMP such as flagellin or chitin is reflected in the very widespread presence of PRRs in higher plants (34). This contrasts with the low cost of virulence and correspondingly low frequency of resistance in the GFG system.

COEVOLUTION IN AGRICULTURE

In nature, *RES* genes can be long-lived, implying they must have had a useful function for thousands or even millions of years (13, 56, 113). In agriculture, by contrast, it has been recognized for almost a century that, with rare exceptions, GFG resistances only control crop diseases for a few years (17, 22). There is increasing evidence that the rates of evolution of *RES* and *AVR* genes throughout the history and prehistory of agriculture have been rapid

(49, 77, 98, 106, 144). Plant-parasite coevolutionary dynamics in nature appear largely to follow the trench warfare model, whereas in agriculture, they take the form of an arms race. Recognition of the reasons why coevolution has become destabilized in agriculture might point to ways of making control of crop diseases more durable.

Many of the factors that generate ndFDS and stabilize genetic diversity in nature are excluded from farming systems. This can be recognized by running through almost all the factors in **Table 1**. Volunteer plants growing from seed banks (see References 29, 122) are not encouraged and are often destroyed as weeds; most major crops are annuals, rather than perennials or biennials (see Reference 122); the life cycles of crops and their pathogens are highly synchronized because large fields contain genetically uniform crop varieties (see Reference 74); farmers seek to achieve a uniform environment capable of predictable crop production, rather than a heterogeneous environment (see References 45, 88); over the last century, many new GFG *RES* genes have been introduced, which is equivalent to a high rate of mutation in the host (see References 62, 99, 126); and large areas of uniform crops and parasite dispersal over large distances (22) mean that host and parasite life cycles are closely coupled, weakening epidemiological feedbacks (see References 39, 44, 53, 122, 126). Although genetically uniform crops allow high rates of autoinfection, with almost all pathogen propagules attacking plants of the same genotype as that on which they were produced (120), autoinfection can be discounted as a factor promoting ndFDS in agriculture because it does so only when there is a high probability of propagules infecting plants that were not previously diseased (**Figure 3**). Meanwhile, the close coupling of host and parasite life cycles strengthens iFDS (22), and human management of resistance gene frequencies drives the coevolution of crops and pathogens to instability (117, 118).

Stability in disease control matters because the purpose of agriculture is to produce large amounts of food of acceptable quality at affordable prices. Diseases detract from this aim, and unpredictable outbreaks of disease are especially troublesome. As we enter an era when the climate is becoming less predictable and the number of pesticides available to farmers is declining, a reasonable goal is for disease control in arable crops to be sufficiently reliable to avoid significant losses of yield and quality. Several approaches to crop management that aim to reduce the speed with which pathogens adapt to crops have been proposed; they include increasing the genetic diversity of crops, which can slow the development of epidemics and reduce the severity of disease (85), breeding for quantitative resistance (54, 112), which is often more durable than GFG resistance because pathogens often adapt more slowly to it if at all, and using resistance genes for which the corresponding parasite virulence has a high cost (69). Although attempts to apply coevolutionary insights to farming systems should always consider that the primary objective of agriculture is to produce food and that disease control is only a means to achieving that end, reducing the speed with which parasites adapt to crops could make a significant contribution to sustaining reliable food production.

SUMMARY POINTS

1. The GFG relationship is a model for the coevolution of parasites and their hosts, especially plants. Principles of coevolution elucidated in the GFG system apply equally to other host defenses, including toxin receptors, guard proteins and basal resistance.
2. Frequencies of host resistance and parasite virulence alleles evolve in the familiar 'boom-and-bust' cycle. Allele cycles are driven by iFDS, in which the contribution of resistance to host fitness depends on the frequency of parasite virulence and vice versa. In simple models, these cycles are unstable and alleles become fixed in the 'arms race' scenario.

3. Long-term, balanced polymorphism can be achieved if there is dFDS, in which the contribution of a resistance (or virulence) allele to fitness decreases as its own frequency increases. This leads to a situation known as 'trench warfare', with quasi-stable, balanced polymorphism in both species. Many ecological and epidemiological factors promote dFDS, the overarching principle being that host and parasite life cycles must be partially decoupled.
4. Over-dominance in outbreeding diploids can also lead to stable polymorphism if a plant with a heterozygous resistance locus has higher fitness than either homozygote in the face of a diverse pathogen population.
5. Fitness costs of resistance and virulence are required to drive coevolutionary cycles but are not sufficient by themselves to stabilize polymorphism. However, higher fitness costs increase the range of values of other parameters over which polymorphism is stable.
6. In addition to deterministic processes in large populations, genetic diversity in hosts and parasites can also take the form of stochastic polymorphism in which localized dispersal, random genetic drift and high mutation rates prevent alleles from becoming fixed.
7. Experiments to test the significance of factors that generate dFDS or overdominance are necessary, but they are challenging because the appropriate experimental units are entire populations, not individual plants and pathogens.
8. Many of the factors that stabilize polymorphism in coevolving hosts and parasites have been lost in agriculture, leading to instability of parasite evolution and unpredictability of disease control.

FUTURE ISSUES

1. There is a great shortage of relevant experimental data. Mathematical models propose hypotheses about the natural world but cannot test them, so while experiments on co-evolution are difficult to design, they are crucial. It would be especially valuable to know which of the many factors that generate ndFDS in models are most significant in nature.
2. To ensure the analysis remains tractable, most models of coevolution assume the host and parasite are haploid. ndFDS is then the only general means of stabilizing polymorphism. While a few studies have indicated that overdominance has a role in stabilizing polymorphism (146), its significance compared to ndFDS has not been assessed.
3. Research on the evolution of plant resistance and pathogen avirulence and effector gene families is accelerating thanks to high-throughput sequencing. Fresh discoveries should be incorporated into models of host-parasite coevolution. For comparison, discoveries of families of effector genes (98, 103) and common pathways of defense (58) were reflected in the structure of costs in a model of multi-locus coevolution (119).
4. Taking points 2 and 3 together, an important topic is further development of the theory of interactions between multiple host and parasite genes. A key question is which conditions lead to arms races, with transient polymorphism successively in many genes, and which to trench warfare, with quasi-stable polymorphism at many loci.

5. The GFG system is better understood than other aspects of plant defense. Incorporation of important features such as partial resistance (54, 112), tolerance (21, 136) and inducible resistance (109, 121, 139) would provide a fuller understanding of the relationship of plant-parasite coevolution to the complete mechanism of plant defense. The evolution of parasite aggressiveness (40, 44) could also be built into GFG models.
6. Almost all models have considered interactions of one plant species with one pathogen species (see Reference 29 for an exception). Yet in both nature and agriculture, plants are assailed by communities of diverse parasite species (10, 130). To understand fully the role of resistance to diseases and pests in nature, we need to understand the evolution of communities of plant and parasite species.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Research on coevolution draws on many fields of biology and we apologize to colleagues whose work we have been unable to cite for reasons of space. J.K.M.B. acknowledges support by the Biotechnology and Biological Sciences Research Council and the European Union Framework 6 project, BioExploit. A.T. acknowledges funding from the Volkswagen Foundation (postdoctoral grant I/82752).

LITERATURE CITED

1. Aguileta G, Refregier G, Yockteng R, Fournier E, Giraud T. 2009. Rapidly evolving genes in pathogens: methods for detecting positive selection and examples among fungi, bacteria, viruses and protists. *Inf. Genet. Evol.* 9:656–70
2. Allen JC. 1975. Mathematical models of species interactions in time and space. *Am. Nat.* 109:319–42
3. Allen RL, Bittner-Eddy PD, Grenville-Briggs LJ, Meitz JC, Rehmany AP, et al. 2004. Host-parasite coevolutionary conflict between *Arabidopsis* and downy mildew. *Science* 306:1957–60
4. Antonovics J, Thrall PH. 1994. The cost of resistance and the maintenance of genetic polymorphism in host-pathogen systems. *Proc. R. Soc. B* 257:105–10
5. Araki H, Tian DC, Goss EM, Jakob K, Halldorsdottir SS, et al. 2006. Presence/absence polymorphism for alternative pathogenicity islands in *Pseudomonas viridiflava*, a pathogen of *Arabidopsis*. *Proc. Natl. Acad. Sci. USA* 103:5887–92
6. Atwell S, Huang YS, Vilhjalmsson BJ, Willems G, Horton M, et al. 2010. Genome-wide association study of 107 phenotypes in *Arabidopsis thaliana* inbred lines. *Nature* 465:627–31
7. Bahri B, Kaltz O, Leconte M, de Vallavieille-Pope C, Enjalbert J. 2009. Tracking costs of virulence in natural populations of the wheat pathogen, *Puccinia striiformis* f. sp. *tritici*. *BMC Evol. Biol.* 9:26
8. Bakker EG, Toomajian C, Kreitman M, Bergelson J. 2006. A genome-wide survey of R gene polymorphisms in *Arabidopsis*. *Plant Cell* 18:1803–18
9. Barrett JA. 1980. Pathogen evolution in multilines and variety mixtures. *Z. Pflanzenkrankh. Pflanzenschutz* 87:383–96
10. Barrett LG, Kniskern JM, Bodenhausen N, Zhang W, Bergelson J. 2009. Continua of specificity and virulence in plant host-pathogen interactions: causes and consequences. *New Phytol.* 183:513–29

11. Barrett LG, Thrall PH, Dodds PN, van der Merwe M, Linde CC, et al. 2009. Diversity and evolution of effector loci in natural populations of the plant pathogen *Melampsora lini*. *Mol. Biol. Evol.* 26:2499–513
12. Bergelson J, Dwyer G, Emerson JJ. 2001. Models and data on plant-enemy coevolution. *Annu. Rev. Genet.* 35:469–99
13. Bergelson J, Kreitman M, Stahl EA, Tian DC. 2001. Evolutionary dynamics of plant R-genes. *Science* 292:2281–85
14. Bergelson J, Purrington CB. 1996. Surveying patterns in the cost of resistance in plants. *Am. Nat.* 148:536–58
15. Bomblies K, Weigel D. 2007. Hybrid necrosis: autoimmunity as a potential gene-flow barrier in plant species. *Nat. Rev. Genet.* 8:382–93
16. Brockhurst MA, Buckling A, Poullain V, Hochberg ME. 2007. The impact of migration from parasite-free patches on antagonistic host-parasite coevolution. *Evolution* 61:1238–43
17. Brown JKM. 1995. Pathogens' responses to the management of disease resistance genes. In *Advances in Plant Pathology, Vol. 11.*, ed. JH Andrews, IC Tommerup, pp. 75–102. London: Academic
18. Brown JKM. 2003. A cost of disease resistance: paradigm or peculiarity? *Trends Genet.* 19:667–71
19. Brown JKM. 2003. Little else but parasites. *Science* 299:1680–81
20. Brown JKM. 2007. Fitness costs of plant disease resistance. In *Handbook of Plant Science*, ed. K Robert, pp. 815–22. Chichester, UK: John Wiley & Sons
21. Brown JKM, Handley RJ. 2006. Evolutionary genetics: fight or flinch? *Heredity* 96:3–4
22. Brown JKM, Hovmøller MS. 2002. Aerial dispersal of pathogens on the global and continental scales and its impact on plant disease. *Science* 297:537–41
23. Burdon JJ, Jarosz AM. 1991. Host-pathogen interactions in natural-populations of *Linum marginale* and *Melampsora lini*. 1. Patterns of resistance and racial variation in a large host population. *Evolution* 45:205–17
24. Caicedo AL, Schaal BA. 2004. Heterogeneous evolutionary processes affect *R* gene diversity in natural populations of *Solanum pimpinellifolium*. *Proc. Natl. Acad. Sci. USA* 101:17444–49
25. Caldo RA, Nettleton D, Peng JQ, Wise RP. 2006. Stage-specific suppression of basal defense discriminates barley plants containing fast- and delayed-acting *Mla* powdery mildew resistance alleles. *Mol. Plant-Microbe Interact.* 19:939–47
26. Campbell CL, Madden LV. 1990. *Introduction to Plant Disease Epidemiology*. New York: Wiley Interscience
27. Clarke B. 1964. Frequency-dependent selection for dominance of rare polymorphic genes. *Evolution* 18:364–69
28. Clarke B. 1976. The ecological genetics of host-parasite relationships. In *Genetic Aspects of Host-Parasite Relationships*, ed. AER Taylor, R Muller, pp. 97–103. Oxford, UK: Blackwell
29. Damgaard C. 1999. Coevolution of a plant host-pathogen gene-for-gene system in a metapopulation model without cost of resistance or cost of virulence. *J. Theor. Biol.* 201:1–12
30. de Meaux J, Cattan-Toupance I, Lavigne C, Langin T, Neema C. 2003. Polymorphism of a complex resistance gene candidate family in wild populations of common bean (*Phaseolus vulgaris*) in Argentina: comparison with phenotypic resistance polymorphism. *Mol. Ecol.* 12:263–73
31. Decaestecker E, Gaba S, Raeymaekers JAM, Stoks R, Van Kerckhoven L, et al. 2007. Host-parasite 'Red Queen' dynamics archived in pond sediment. *Nature* 450:870–73
32. Dodds PN, Lawrence GJ, Catanzariti AM, Teh T, Wang CIA, et al. 2006. Direct protein interaction underlies gene-for-gene specificity and coevolution of the flax resistance genes and flax rust avirulence genes. *Proc. Natl. Acad. Sci. USA* 103:8888–93
33. Dodds PN, Rathjen JP. 2010. Plant immunity: towards an integrated view of plant-pathogen interactions. *Nat. Rev. Genet.* 11:539–48
34. Dunning FM, Sun W, Jansen KL, Helft L, Bent AF. 2007. Identification and mutational analysis of *Arabidopsis* FLS2 leucine-rich repeat domain residues that contribute to flagellin perception. *Plant Cell* 19:3297–313
35. Fenton A, Antonovics J, Brockhurst MA. 2009. Inverse-gene-for-gene infection genetics and coevolutionary dynamics. *Am. Nat.* 174:E230–42

36. Fleming RA. 1980. Selection pressures and plant-pathogens—robustness of the model. *Phytopathology* 70:175–78
37. Flor HH. 1971. Current status of gene-for-gene concept. *Annu. Rev. Phytopathol.* 9:275–96
38. Frank SA. 1992. Models of plant pathogen coevolution. *Trends Genet.* 8:213–19
39. Frank SA. 1993. Coevolutionary genetics of plants and pathogens. *Evol. Ecol.* 7:45–75
40. Frank SA. 1994. Coevolutionary genetics of hosts and parasites with quantitative inheritance. *Evol. Ecol.* 8:74–94
41. Gandon S, Buckling A, Decaestecker E, Day T. 2008. Host-parasite coevolution and patterns of adaptation across time and space. *J. Evol. Biol.* 21:1861–66
42. Gandon S, Capowiez Y, Dubois Y, Michalakis Y, Olivieri I. 1996. Local adaptation and gene-for-gene coevolution in a metapopulation model. *Proc. R. Soc. Lond. B* 263:1003–9
43. Gandon S, Nuismer SL. 2009. Interactions between genetic drift, gene flow, and selection mosaics drive parasite local adaptation. *Am. Nat.* 173:212–24
44. Gandon S, van Baalen M, Jansen VAA. 2002. The evolution of parasite virulence, superinfection, and host resistance. *Am. Nat.* 159:658–69
45. Gavrilets S, Michalakis Y. 2008. Effects of environmental heterogeneity on victim-exploiter coevolution. *Evolution* 62:3100–16
46. Gilligan CA. 1983. Modeling of soilborne pathogens. *Annu. Rev. Phytopathol.* 21:45–64
47. Giraud T, Gladieux P, Gavrilets S. 2010. Linking the emergence of fungal plant diseases with ecological speciation. *Trends Ecol. Evol.* 25:387–95
48. Guo M, Tian F, Wamboldt Y, Alfano JR. 2009. The majority of the type III effector inventory of *Pseudomonas syringae* pv. *tomato* DC3000 can suppress plant immunity. *Mol. Plant-Microbe Interact.* 22:1069–80
49. Haas BJ, Kamoun S, Zody MC, Jiang RHY, Handsaker RE, et al. 2009. Genome sequence and analysis of the Irish potato famine pathogen *Phytophthora infestans*. *Nature* 461:393–98
50. Haldane JBS. 1949. Disease and evolution. *Ric. Sci.* 19:68–76
51. Hamilton WD. 1980. Sex versus non-sex versus parasite. *Oikos* 35:282–90
52. Holub EB. 2001. The arms race is ancient history in *Arabidopsis*, the wildflower. *Nat. Rev. Genet.* 2:516–27
53. Jeger MJ. 1997. An epidemiological approach to modeling the dynamics of gene-for-gene interactions. In *The Gene-for-Gene Relationship*, ed. IR Crute, EB Holub, JJ Burdon, pp. 191–209. Wallingford, UK: CABI
54. Johnson R. 1984. A critical analysis of durable resistance. *Annu. Rev. Phytopathol.* 22:309–30
55. Jones JDG, Dangl JL. 2006. The plant immune system. *Nature* 444:323–29
56. Jordan T, Seeholzer S, Schwizer S, Keller B. 2011. The wheat *Mla* homolog *TmMla1* exhibits an evolutionary conserved function against powdery mildew in both wheat and barley. *Plant J.* 65:610–21
57. Karlin S, McGregor J. 1972. Polymorphisms for genetic and ecological systems with weak coupling. *Theor. Pop. Biol.* 3:210–38
58. Katagiri F, Tsuda K. 2010. Understanding the plant immune system. *Mol. Plant-Microbe Interact.* 23:1531–36
59. Kawecki TJ, Ebert D. 2004. Conceptual issues in local adaptation. *Ecol. Lett.* 7:1225–41
60. Kesinger JC, Allen LJS. 2002. Genetic models for plant pathosystems. *Math. Biosci.* 177:247–69
61. Kesinger JC, Allen LJS, Strauss RE. 2001. Discrete-time models for gene frequencies and population densities in plant pathosystems. *Nonlinear Anal.-Theory Methods Appl.* 47:1489–500
62. Kirby GC, Burdon JJ. 1997. Effects of mutation and random drift on Leonard's gene-for-gene coevolution model. *Phytopathology* 87:488–93
63. Korves T, Bergelson J. 2004. A novel cost of *R* gene resistance in the presence of disease. *Am. Nat.* 163:489–504
64. Laine AL. 2004. Resistance variation within and among host populations in a plant-pathogen metapopulation: implications for regional pathogen dynamics. *J. Ecol.* 92:990–1000
65. Laine AL. 2006. Evolution of host resistance: looking for coevolutionary hotspots at small spatial scales. *Proc. R. Soc. B* 273:267–73

66. Laine AL. 2008. Temperature-mediated patterns of local adaptation in a natural plant-pathogen metapopulation. *Ecol. Lett.* 11:327–37
67. Laine AL. 2009. Role of coevolution in generating biological diversity: spatially divergent selection trajectories. *J. Exp. Bot.* 60:2957–70
68. Laine AL, Tellier A. 2008. Heterogeneous selection promotes maintenance of polymorphism in host-parasite interactions. *Oikos* 117:1281–88
69. Leach JE, Cruz CMV, Bai JF, Leung H. 2001. Pathogen fitness penalty as a predictor of durability of disease resistance genes. *Annu. Rev. Phytopathol.* 39:187–224
70. Leonard KJ. 1969. Genetic equilibria in host-pathogen systems. *Phytopathology* 59:1858–63
71. Leonard KJ. 1977. Selection pressures and plant pathogens. *Ann. N. Y. Acad. Sci.* 287:207–22
72. Leonard KJ. 1994. Stability of equilibria in a gene-for-gene coevolution model of host-parasite interactions. *Phytopathology* 84:70–77
73. Leonard KJ, Czochor RJ. 1978. Response to selection pressures and plant pathogens stability of equilibria. *Phytopathology* 68:971–73
74. Leonard KJ, Czochor RJ. 1980. Theory of genetic interactions among populations of plants and their pathogens. *Annu. Rev. Phytopathol.* 18:237–58
75. Levene H. 1953. Genetic equilibrium when more than one ecological niche is available. *Am. Nat.* 87:331–33
76. Lewontin R. 1958. A general method for investigating the equilibrium of gene frequency in a population. *Genetics* 43:419–34
77. Li J, Ding J, Zhang W, Zhang YL, Tang P, et al. 2010. Unique evolutionary pattern of numbers of gramineous NBS-LRR genes. *Mol. Genet. Genomics* 283:427–38
78. Little TJ, Watt K, Ebert D. 2006. Parasite-host specificity: experimental studies on the basis of parasite adaptation. *Evolution* 60:31–38
79. May RM. 1972. Limit cycles in predator-prey communities. *Science* 177:900–02
80. Meyers BC, Chin DB, Shen KA, Sivaramakrishnan S, Lavelle DO, et al. 1998. The major resistance gene cluster in lettuce is highly duplicated and spans several megabases. *Plant Cell* 10:1817–32
81. Michelmore RW, Meyers BC. 1998. Clusters of resistance genes in plants evolve by divergent selection and a birth-and-death process. *Genome Res.* 8:1113–30
82. Mode CJ. 1958. A mathematical model for the co-evolution of obligate parasites and their hosts. *Evolution* 12:158–65
83. Montarry J, Hamelin FM, Glais I, Corbière R, Andrivon D. 2010. Fitness costs associated with unnecessary virulence factors and life history traits: evolutionary insights from the potato late blight pathogen *Phytophthora infestans*. *BMC Evol. Biol.* 10:283
84. Morgan AD, Gandon S, Buckling A. 2005. The effect of migration on local adaptation in a coevolving host-parasite system. *Nature* 437:253–56
85. Mundt CC. 2002. Use of multiline cultivars and cultivar mixtures for disease management. *Annu. Rev. Phytopathol.* 40:381–410
86. Nemri A, Atwell S, Tarone AM, Huang YS, Zhao K, et al. 2010. Genome-wide survey of *Arabidopsis* natural variation in downy mildew resistance using combined association and linkage mapping. *Proc. Natl. Acad. Sci. USA* 107:10302–7
87. Nowara D, Gay A, Lacomme C, Shaw J, Ridout C, et al. 2010. HIGS: Host-induced gene silencing in the obligate biotrophic fungal pathogen *Blumeria graminis*. *Plant Cell* 22:3130–41
88. Nuismer SL. 2006. Parasite local adaptation in a geographic mosaic. *Evolution* 60:24–30
89. Nuismer SL, Gandon S. 2008. Moving beyond common-garden and transplant designs: insight into the causes of local adaptation in species interactions. *Am. Nat.* 171:658–68
90. Oldroyd GED, Staskawicz BJ. 1998. Genetically engineered broad-spectrum disease resistance in tomato. *Proc. Natl. Acad. Sci. USA* 95:10300–5
91. Parker IM, Gilbert GS. 2004. The evolutionary ecology of novel plant-pathogen interactions. *Annu. Rev. Ecol. Evol. Syst.* 35:675–700
92. Person C. 1966. Genetic polymorphism in parasitic systems. *Nature* 212:266–67

93. Ridout CJ, Skamnioti P, Porritt O, Sacristan S, Jones JDG, Brown JKM. 2006. Multiple avirulence paralogues in cereal powdery mildew fungi may contribute to parasite fitness and defeat of plant resistance. *Plant Cell* 18:2402–14
94. Rose LE, Langley CH, Bernal AJ, Michelmore RW. 2005. Natural variation in the *Pto* pathogen resistance gene within species of wild tomato (*Lycopersicon*). I. Functional analysis of *Pto* alleles. *Genetics* 171:345–57
95. Rose LE, Michelmore RW, Langley CH. 2007. Natural variation in the *Pto* pathogen resistance gene within species of wild tomato (*Lycopersicon*). II. Population genetics of *Pto*. *Genetics* 175:1307–19
96. Roux F, Gao LP, Bergelson J. 2010. Impact of initial pathogen density on resistance and tolerance in a polymorphic disease resistance gene system in *Arabidopsis thaliana*. *Genetics* 185:283–91
97. Sacristan S, Garcia-Arenal F. 2008. The evolution of virulence and pathogenicity in plant pathogen populations. *Mol. Plant Pathol.* 9:369–84
98. Sacristan S, Vigouroux M, Pedersen C, Skamnioti P, Thordal-Christensen H, et al. 2009. Coevolution between a family of parasite virulence effectors and a class of LINE-1 retrotransposons. *PLoS ONE* 4:e7463
99. Salathe M, Scherer A, Bonhoeffer S. 2005. Neutral drift and polymorphism in gene-for-gene systems. *Ecol. Lett.* 8:925–32
100. Salvaudon L, Giraud T, Shykoff JA. 2008. Genetic diversity in natural populations: a fundamental component of plant-microbe interactions. *Curr. Opin. Plant Biol.* 11:1–9
101. Sasaki A. 2000. Host-parasite coevolution in a multilocus gene-for-gene system. *Proc. R. Soc. B* 267:2183–88
102. Sasaki A, Hamilton WD, Ubeda F. 2002. Clone mixtures and a pacemaker: new facets of Red-Queen theory and ecology. *Proc. R. Soc. Lond. B* 269:761–72
103. Schornack S, van Damme M, Bozkurt TO, Cano LM, Smoker M, et al. 2010. Ancient class of translocated oomycete effectors targets the host nucleus. *Proc. Natl. Acad. Sci. USA* 107:17421–26
104. Schwessinger B, Zipfel C. 2008. News from the frontline: recent insights into PAMP-triggered immunity in plants. *Curr. Opin. Plant Biol.* 11:389–95
105. Sedcole JR. 1978. Selection pressures and plant pathogens—stability of equilibria. *Phytopathology* 68:967–70
106. Seeholzer S, Tsuchimatsu T, Jordan T, Bieri S, Pajonk S, et al. 2010. Diversity at the *Mla* powdery mildew resistance locus from cultivated barley reveals sites of positive selection. *Mol. Plant-Microbe Interact.* 23:497–509
107. Segarra J. 2005. Stable polymorphisms in a two-locus gene-for-gene system. *Phytopathology* 95:728–36
108. Seger J. 1988. Dynamics of some simple host-parasite models with more than 2 genotypes in each species. *Philos. Trans. R. Soc. B* 319:541–55
109. Shoresh M, Harman GE, Mastouri F. 2010. Induced systemic resistance and plant responses to fungal biocontrol agents. *Annu. Rev. Phytopathol.* 48:21–43
110. Soubeyrand S, Laine AL, Hanski I, Penttinen A. 2009. Spatiotemporal structure of host-pathogen interactions in a metapopulation. *Am. Nat.* 174:308–20
111. Spanu PD, Abbott JC, Amselem J, Burgis TA, Soanes DM, et al. 2010. Genome expansion and gene loss in powdery mildew fungi reveal functional tradeoffs in parasitism. *Science* 330:1543–46
112. St. Clair DA. 2010. Quantitative disease resistance and quantitative resistance loci in breeding. *Annu. Rev. Phytopathol.* 48:247–68
113. Stahl EA, Dwyer G, Mauricio R, Kreitman M, Bergelson J. 1999. Dynamics of disease resistance polymorphism at the *Rpm1* locus of *Arabidopsis*. *Nature* 400:667–71
114. Stukenbrock EH, McDonald BA. 2007. Geographical variation and positive diversifying selection in the host-specific toxin SnToxA. *Mol. Plant Pathol.* 8:321–32
115. Stukenbrock EH, McDonald BA. 2008. The origins of plant pathogens in agro-ecosystems. *Annu. Rev. Phytopathol.* 46:75–100
116. Stukenbrock EH, McDonald BA. 2009. Population genetics of fungal and oomycete effectors involved in gene-for-gene interactions. *Mol. Plant-Microbe Interact.* 22:371–80
117. Sun P, Yang XB. 1998. Stability of a gene-for-gene coevolution system under constant perturbations. *Phytopathology* 88:592–97

118. Sun P, Yang XB. 1999. Two properties of a gene-for-gene coevolution system under human perturbations. *Phytopathology* 89:811–16
119. Tellier A, Brown JKM. 2007. Polymorphism in multilocus host-parasite coevolutionary interactions. *Genetics* 177:1777–90
120. Tellier A, Brown JKM. 2007. Stability of genetic polymorphism in host-parasite interactions. *Proc. R. Soc. B* 274:809–17
121. Tellier A, Brown JKM. 2008. The relationship of host-mediated induced resistance to polymorphism in gene-for-gene relationships. *Phytopathology* 98:128–36
122. Tellier A, Brown JKM. 2009. The influence of perenniality and seed banks on polymorphism in plant-parasite interactions. *Am. Nat.* 174:769–79
123. Thompson JN. 1999. Specific hypotheses on the geographic mosaic of coevolution. *Am. Nat.* 153:S1–S14
124. Thompson JN. 2005. *The Geographic Mosaic of Coevolution*. Chicago, IL: Univ. Chicago Press
125. Thompson JN, Burdon JJ. 1992. Gene-for-gene coevolution between plants and parasites. *Nature* 360:121–25
126. Thrall PH, Burdon JJ. 2002. Evolution of gene-for-gene systems in metapopulations: the effect of spatial scale of host and pathogen dispersal. *Plant Pathol.* 51:169–84
127. Thrall PH, Burdon JJ. 2003. Evolution of virulence in a plant host-pathogen metapopulation. *Science* 299:1735–37
128. Thrall PH, Burdon JJ, Bever JD. 2002. Local adaptation in the *Linum marginale–Melampsora lini* host-pathogen interaction. *Evolution* 56:1340–51
129. Thrall PH, Burdon JJ, Bock CH. 2001. Short-term epidemic dynamics in the *Cakile maritima–Alternaria brassicicola* host-pathogen association. *J. Ecol.* 89:723–35
130. Thrall PH, Hochberg ME, Burdon JJ, Bever JD. 2007. Coevolution of symbiotic mutualists and parasites in a community context. *Trends Ecol. Evol.* 22:120–26
131. Tian D, Traw MB, Chen JQ, Kreitman M, Bergelson J. 2003. Fitness costs of R-gene-mediated resistance in *Arabidopsis thaliana*. *Nature* 423:74–77
132. Tsuda K, Sato M, Stoddard T, Glazebrook J, Katagiri F. 2009. Network properties of robust immunity in plants. *PLoS Genet.* 5:e1000772
133. van der Biezen EA, Jones JDG. 1998. Plant disease–resistance proteins and the gene-for-gene concept. *Trends Biochem. Sci.* 23:454–56
134. van der Hoorn RAL, De Wit P, Joosten M. 2002. Balancing selection favors guarding resistance proteins. *Trends Plant Sci.* 7:67–71
135. van der Merwe MM, Kinnear MW, Barrett LG, Dodds PN, Ericson L, et al. 2009. Positive selection in *AvrP4* avirulence gene homologues across the genus *Melampsora*. *Proc. Roy. Soc. B* 276:2913–22
136. van der Meijden E, Wijn M, Verkaar HJ. 1988. Defense and regrowth, alternative plant strategies in the struggle against herbivores. *Oikos* 51:355–63
137. Vanderplank JE. 1968. *Disease Resistance in Plants*. New York: Academic 206 pp.
138. Vera Cruz CM, Bai JF, Ona I, Leung H, Nelson RJ, et al. 2000. Predicting durability of a disease resistance gene based on an assessment of the fitness loss and epidemiological consequences of avirulence gene mutation. *Proc. Natl. Acad. Sci. USA* 97:13500–5
139. Vlot AC, Dempsey DMA, Klessig DF. 2009. Salicylic acid, a multifaceted hormone to combat disease. *Annu. Rev. Phytopathol.* 47:177–206
140. Wei FS, Wong RA, Wise RP. 2002. Genome dynamics and evolution of the *Mla* (powdery mildew) resistance locus in barley. *Plant Cell* 14:1903–17
141. Wichmann G, Bergelson J. 2004. Effector genes of *Xanthamonas axonopodis* pv. *vesicatoria* promote transmission and enhance other fitness traits in the field. *Genetics* 166:693–706
142. Wilfert L, Jiggins FM. 2010. Host-parasite coevolution: genetic variation in a virus population and the interaction with a host gene. *J. Evol. Biol.* 23:1447–55
143. Woolhouse MEJ, Webster JP, Domingo E, Charlesworth B, Levin BR. 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nat. Genet.* 32:569–77
144. Yahiaoui N, Brunner S, Keller B. 2006. Rapid generation of new powdery mildew resistance genes after wheat domestication. *Plant J.* 47:85–98

145. Yahiaoui N, Kaur N, Keller B. 2009. Independent evolution of functional Pm3 resistance genes in wild tetraploid wheat and domesticated bread wheat. *Plant J.* 57:846–56
146. Ye TZ, Yang RC, Yeh FC. 2003. Coevolution in natural pathosystems: effects of dominance on host-pathogen interactions. *Phytopathology* 93:633–39
147. Zipfel C. 2008. Pattern-recognition receptors in plant innate immunity. *Curr. Opin. Immunol.* 20:10–16

Annual Review of Phytopathology

Volume 49, 2011

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Errata

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