The Relationship of Host-Mediated Induced Resistance to Polymorphism in Gene-for-Gene Relationships

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ABSTRACT

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Gene-for-gene relationships are a common feature of plant-parasite interactions. Polymorphism at host resistance and parasite avirulence loci is maintained if there is negative, direct frequency-dependent selection on alleles of either gene. More specifically, selection of this kind is generated when the disease is polycyclic with frequent auto-infection. When an incompatible interaction occurs between a resistant host and an avirulent parasite, systemic defenses are triggered, rendering the plant more resistant to a later attack by another parasite. However, induced resistance (IR) incurs a fitness cost to the plant. Here, the effect of IR on polymorphism in gene-for-gene interactions is investigated. First, in an

infinite population model in which parasites have two generations per host generation, increasing the fitness cost of IR increases selection for susceptible plants at low disease severity, while increasing the effectiveness of IR against further parasite attacks enhances selection for resistant plants at high disease severity. This reduces the possibility of polymorphism being maintained in host and parasite populations. In finite population models, the number of plants varies over time as a function of the disease burden of the population. Polymorphism in gene-for-gene relationships is then more stable at high disease prevalence and severity if IR reactions are more costly when there is competition for resources between plants.

Additional keywords: coevolution, epidemiological models, natural selection, resistance, virulence.

Gene-for-gene (GFG) relationships govern many plant-parasite interactions (1,8,15,24). In the simplest case, a host resistance (*RES*) locus interacts with a corresponding parasite avirulent (*AVR*) locus. Effective defenses are induced if a plant has a *RES* gene enabling recognition of a specific parasite *AVR* gene (15). The parasite is not detected by the host and defenses are not induced if the host has a susceptibility allele (*res*) or the parasite has a virulence allele (*avr*). Genetically, the *RES* and *AVR* alleles are usually dominant.

The asymmetry of the GFG interaction suggests that in the absence of other factors, there will be an “arms race”, as successive pairs of *RES* and *AVR* alleles are driven to fixation in host and parasite populations, respectively (24). In nature, however, there is substantial polymorphism at *RES* and *AVR* loci both within populations and across spatially structured subpopulations (44,49,50). The fact that some of these polymorphisms are ancient (1,34,50,52) supports the “trench warfare” group of models in which polymorphism is quasi-stable (44), in contrast to the transient polymorphism in “arms race” models (24).

Several mathematical models have been formulated to understand the coevolutionary process in single-locus (30,33,46) or multilocus GFG systems (41–43). Coevolution implies the existence of indirect frequency-dependent selection (FDS), because the rate of natural selection on a host allele depends on the frequency of a corresponding parasite allele, and vice-versa (20). Most theoretical studies predict the existence of constitutive costs of *RES* and *avr* alleles in order to counteract selection by the parasite or host, respectively (4,20,30,31,33). Some experiments have detected such costs (29,48,51,53), but others have not (5–

7,15,53). Costs of *RES* and *avr* alleles are necessary but not sufficient to maintain stable long term polymorphism at host and parasite loci (46). However, increasing constitutive fitness costs of *RES* reinforces indirect FDS because it reduces selection for *RES* when the frequency of *AVR* is high, and enhances selection against *RES* when the frequency of *avr* is high (similarly, increasing the constitutive cost of *avr* reduces net selection for *avr*) (4,20,30,33,46).

Polymorphism can be maintained in both host and parasite populations only if there is also negative, direct FDS, such that the strength of natural selection for either *RES* or *avr* or both, declines with increasing frequency of that allele (46). This general condition encompasses numerous factors previously proposed to account for polymorphism at corresponding GFG loci such as biological characteristics of plants (perenniality or seed banks) and environmental heterogeneity (46).

Most plant diseases are polycyclic, as the parasite passes through more than one generation on the same plant. This also helps to stabilize polymorphism in GFG systems (46). In a polycyclic disease, the stability of GFG systems depends on the outcome of infection in one parasite generation influencing the next parasite generation. As a plant grows, each new leaf may be infected by a spore produced either on the same plant or on another plant (auto-infection and allo-infection, respectively) (3). Increasing the rate of auto-infection tends to enhance the stability of polymorphism in GFG systems (46).

Here, the influence of an important characteristic of polycyclic diseases, host-mediated interactions between parasite genotypes, on GFG coevolution is investigated. An *RES* plant is not only constitutively resistant to *AVR* parasites by a GFG interaction, but may also express induced resistance (IR) against further attack by parasites, whether *AVR* or *avr* (19,26,28,40). Two important types of IR are known, systemic acquired resistance (SAR), mediated by salicylate (19,26,40,45), and induced systemic resistance

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(ISR), mediated by jasmonate and ethylene (38,45). Induction of IR involves a significant metabolic fitness cost for plants (13, 17,18,21-23), the size of which depends on biotic and abiotic conditions of plant growth such as within-species competition for resources or nitrogen availability in the environment (2,11,12, 17,18,22,23,39). Inducibility of defense has two probable advantages: first, the benefit of reducing further attack by parasites is normally greater than the cost of IR (2), and second, the cost of inducible defenses is only incurred when those defenses are activated (in contrast to constitutive costs of *RES* alleles) (11,13). Here, two main parameters are used to describe IR: the cost of inducing it (γ), and its effectiveness in reducing damage by further parasite attack (η).

It has been proposed that IR may be a useful component of control of crop diseases with GFG relationships, for example in variety mixtures in which plants may be attacked successively by virulent and avirulent pathogens (10,37). IR is currently exploited in the control of some virus diseases, notably tristeza of citrus trees (36,54). It is assumed that IR will provide the short-term benefits in terms of reducing the rate of parasite increase but it is important to understand its effects on evolution of the parasite population if it is to be deployed as a component of a long-term strategy of disease control.

In this paper, it is shown that IR tends to reduce the likelihood of maintaining stable polymorphism in GFG interactions in co-evolving host and parasite populations. In model A, an infinite population model is analyzed to investigate the strength of selection due to IR. Model B then uses a deterministic finite population with polycyclic disease, extending model A and developing previous work on infinite populations (46). Moving from infinite to finite population models captures plant population dynamics more realistically, as plant populations have finite numbers of individuals which occupy limited space and compete for resources. Note, however, that relaxing the assumption of competition among plants, for example, when populations become very large both types of model (finite and infinite) show the same behavior. Model B can also be used to investigate the effect of environmental conditions on the cost of IR, as has been demonstrated experimentally (2,11,12,17,18,22,23,39), and thus on the stability of GFG coevolution.

THEORY AND APPROACHES

Model description. Model A is a simplified version of that in (30). The design of the model is similar to (46) in which disease

is polycyclic, with $G > 1$ asexual generations of the parasite per host generation (9). Parameters used in the models are listed in Table 1. For simplicity, it is assumed that *AVR* parasites are completely unable to infect *RES* plants so *RES* plants which encounter *AVR* parasites experience no loss of fitness. At the start of host generation g , each plant is attacked by one parasite of a genotype in proportion to its frequency (A_g for *AVR* and a_g for *avr*). $A_{g,1}$ ($a_{g,1}$) is the *AVR* (*avr*) allele frequency at the end of the first parasite generation ($g,1$) during host generation g . A feature of polycyclic disease is that the outcome of the second parasite generation $g,2$ depends on the result of host-parasite interactions in parasite generation $g,1$ (Table 2). Three types of interactions can occur. First, *RES* plants which encounter *AVR* in parasite generation $g,1$ can be attacked subsequently by any parasite genotype, but *AVR* parasites at the start of generation $g,2$ are still unable to infect *RES* plants (Table 2). Second, *RES* plants attacked by *avr* parasites at the start of $g,1$ remain infected by *avr* parasites in $g,2$. This is because *AVR* parasites are unable to infect *RES* plants successfully. Thirdly, on *res* plants, new leaves produced after the first parasite generation may be infected by a parasite of either genotype, independent of the genotype that infected the older leaves. As a result, only the final parasite generation (g,G) contributes to the population at the start of host generation $g + 1$ (Table 2).

The loss of plant reproductive output caused by disease increases disproportionately with π , the number of successful parasite generations on a host plant ($\pi \leq G$), because as the parasite grows multiplicatively, corresponding damage is done to the host (9). The plant fitness (F) is a decreasing function of π , where z is a parameter defining the shape of the disease curve ($z > 1$). ϕ is the maximum cost to a plant of being diseased after G successful parasite generations (ϵ is the cost for a plant of being infected once) (46).

$$F = 1 - \phi(\pi / G)^z \quad (1)$$

For simplicity, the parasite's reproductive fitness does not depend on π , and $z = 1.4$ (46). ϕ is the reduction in plant seed production, measured in the same units as u , the cost of the *RES* allele.

Recurrence equations for changes in gene frequencies (equations 2 through 4) are obtained from the host and parasite fitnesses in Table 2 with $G = 2$. As an example, the *avr* population at the end of $g,2$ (denominator of equation 3) is the sum of (i) *avr* parasites infecting *RES* plants in generation $g,2$ after an unsuccessful

TABLE 1. Summary of notation

Notation	Definition
R_g (r_g)	Frequency of <i>RES</i> (<i>res</i>) allele at generation g in infinite population model A or number of <i>RES</i> (<i>res</i>) plants in finite population model B
a_g (A_g)	Frequency of <i>avr</i> (<i>AVR</i>) allele at generation g in infinite population model A or number of <i>avr</i> (<i>AVR</i>) plants in finite population model B
X_1 (X_2)	Number of <i>RES</i> (<i>res</i>) healthy plants after parasite generation $g,1$ (model B)
Y_1	<i>RES</i> plants infected by <i>avr</i> parasite after parasite generation $g,1$ (model B)
Y_2 (Y_3)	<i>res</i> plants infected by <i>avr</i> (<i>AVR</i>) strains at generation g (model B)
Y_4	<i>RES</i> plants challenged by <i>AVR</i> parasite after parasite generation $g,1$ (model B)
ϕ	Maximum cost to a plant of being diseased after G successful parasite generations
ϵ	Cost to a plant of being infected once
u	Cost to a plant of having a <i>RES</i> allele (fixed value = 0.05)
b	Cost to a parasite of having an <i>avr</i> allele (fixed value = 0.05)
γ_1 (γ_2)	Cost of triggering induced resistance (IR) once (twice) in a <i>RES</i> plant after one (two) <i>AVR</i> challenge(s)
η	Effectiveness of IR in reducing fitness of next parasite challenger
π	Number of successful parasite generations on a host plant
ρ	Rate of infection of the primary inoculum (model B)
β	Probability of parasite transmission between plants (model B)
ψ	Auto-infection rate (model B)
δ_0	Maximum per capita spore production (fixed value = 5)
θ_0	Maximum per capita spore production (fixed value = 5)
ζ_H (ζ_P)	Strength of plant (parasite) density-dependence regulation (fixed value = 0.004)
$N_{\max}$	Maximum plant population size (fixed value = 1,000)
$\gamma_{\max}$	Maximum cost of expressing IR at maximum plant population size

successful *AVR* parasite attack in $g,1$ ($R_g A_g a_{g,1}$), (ii) *avr* parasites produced in $g,1$ reinfesting the same *RES* plant in $g,2$ ($R_g a_g$), and (iii) *avr* parasites in $g,2$ out-competing *avr* or *AVR* parasites which infected *res* plants in $g,1$ ($r_g a_{g,1} (A_g + a_g)$).

$$\frac{A_{g+1}}{a_{g+1}} = \frac{A_g (1 - R_g)}{a_g (1 - b)} \quad (2)$$

$$\frac{A_{g+1}}{a_{g+1}} = \frac{r_g A_{g,1}}{(1-b) [R_g ((1-\eta) A_g a_{g,1} + a_g) + r_g a_{g,1}]} \quad (3)$$

$$\frac{R_{g+1}}{r_{g+1}} = \frac{(1-u) R_g [A_g A_{g,1} (1-\gamma_2) + A_g a_{g,1} (1-\gamma_1) (1-\varepsilon) + a_g (1-\phi)]}{r_g (1-\phi)} \quad (4)$$

As in Tellier and Brown (46), u and b are constitutive costs of *RES* and *avr* alleles, respectively. Expression of IR in *RES* plants is triggered by any *AVR* parasite attack. This defense reaction is active against every following infection, and reduces the fitness of the next parasite challenger (*avr* or *AVR*) by a proportion η . After induction by an *AVR* parasite, IR is effective during an entire plant generation (27). The cost of IR for the *RES* plant is assumed to be a function of the number of successive *AVR* challenges (16). γ_1 is the cost of triggering IR once in a *RES* plant after one *AVR* challenge, γ_2 is the cost of IR after two *AVR* challenges (Table 2) and $\gamma_1 < \gamma_2$ (16).

RESULTS

Model A: Analysis with $G = 2$ parasite generations. It was not possible to find exact analytical solutions of the nonlinear system of equations 2 to 4 but approximate solutions were found by neglecting quadratic terms of u and b , which are assumed to be small, in accordance with experimental data (5,7). At the non-trivial, interior equilibrium, virulence ($\hat{a} = a_{g+1} = a_g$) and resistance ($\hat{R} = R_{g+1} = R_g$) frequencies are approximately

$$\hat{a} = \frac{\varepsilon + \phi + 2\gamma_2 + \gamma_1 - \sqrt{(\gamma_2 + \gamma_1 + \varepsilon + \phi)^2 - 4(\phi - u - \gamma_2)(\varepsilon + \gamma_2 + \gamma_1)}}{2(1-u)(\varepsilon + \gamma_2 + \gamma_1)} \quad (5)$$

$$\hat{R} = \frac{2b}{3 - b - \eta + b\eta - \hat{a}(1 - \eta + b\eta)} \quad (6)$$

Using equations 2 through 4, the dynamical system can be rewritten by neglecting small quadratic terms (assuming that u^2 , b^2 , and ub are much smaller than 1) in the form of logits of *RES* and *AVR* frequencies ($\Delta f_R = \log(R_{g+1}/r_{g+1}) - \log(R_g/r_g)$; note that Δf_R would be constant if the intensity of natural selection were independent of gene frequencies). The logit transformation makes the algebra much more tractable.

$$\begin{aligned} \Delta f_R &= \log((1-u)/(1-\phi)(1-ba_g)) \\ &+ \log(1 + \gamma_2 - ba_g - a_g A_g (\varepsilon(1-b) + \gamma_1(1-b)(1-\varepsilon)) - a_g (\phi - 2\gamma_2) + a_g^2 (\phi b + \gamma_2)) \\ \Delta f_A &= 2\log(1 - R_g) - \log(1 - b) - \log(1 - b + R_g(1 - a_g)(1 - \eta)) \end{aligned}$$

The system is linearized close to the equilibrium point (equations 5 and 6). Given that $\partial R/\partial f_R = R_g(1 - R_g)$ and $\partial A/\partial f_A = A_g(1 - A_g)$, the elements of the Jacobian matrix J can be found approximately, $\partial \Delta f_R/\partial f_R = 0$, implying that the intensity of natural selection for the *RES* allele does not depend on the frequency of *RES*.

$$\frac{\partial \Delta f_R}{\partial f_A} = A_g \left(\frac{-b}{1 - ba_g} + \frac{b(1 - \varepsilon - \gamma_1(1 - \varepsilon) - 2a_g(\varepsilon + \gamma_1(1 - \varepsilon)) - \gamma_1 - 2a_g(\gamma_1 + \varepsilon) + \phi + 2\gamma_2 + \varepsilon(1 + \gamma_1))}{1 - ba_g + \gamma_2 - a_g A_g (\varepsilon(1 - b) + \gamma_1(1 - b)(1 - \varepsilon)) - a_g (\phi - 2\gamma_2)} \right) \quad (7)$$

This expression is the rate of natural selection for the *RES* allele as a function of the frequency of *AVR*, and is always positive. The costs of IR (γ_1 and γ_2) reduce selection for *RES* compared with a situation where $\gamma_1 = \gamma_2 = 0$ (46). In other words, when the cost of IR increases, the value of $\partial \Delta f_R/\partial f_A$ diminishes but is still positive. Hence, selection for *RES* increases when the frequency of *AVR* is higher but is attenuated by costly IR.

Turning to selection acting on the pathogen,

$$\frac{\partial \Delta f_A}{\partial f_A} = \frac{R_g (\eta - \eta b - 1) A_g a_g}{1 - b + R_g A_g (1 - \eta)} \quad (8)$$

This expression is negative because $\eta(1 - b) < 1$. Hence, direct FDS acts on *AVR* such that selection against *AVR* depends on its own frequency. The value of this expression is less negative (hence, direct FDS is weaker) when η , the effectiveness of IR, increases.

$$\frac{\partial \Delta f_A}{\partial f_R} = R_g (1 - R_g) \left(\frac{-2}{1 - R_g} - \frac{A_g (1 - \eta)}{1 - b + R_g A_g (1 - \eta)} \right) \quad (9)$$

This expression is negative, but is less negative when η increases. Hence, selection against *AVR* increases when the frequency of *RES* is higher but is attenuated by effective IR. When there is no IR ($\gamma_1 = \gamma_2 = \eta = 0$), these results collapse to those in (46).

The stability of the polymorphic equilibrium state depends on the strength of direct FDS against indirect FDS (46). Equation 8 shows that direct FDS, a necessary but not sufficient condition for stable polymorphism, occurs in polycyclic disease. In biological terms, direct FDS occurs ($\partial \Delta f_A/\partial f_A < 0$) because *RES* plants infected by *avr* in $g,1$ remain infected in $g,2$. When a is high, most *RES* plants are *avr*-infected in $g,1$ and remain so in $g,2$. *avr* parasites therefore persist on *RES* plants and are not replaced by *AVR* parasites. On the other hand, when A is high (and a is low), most *RES* plants infected by *avr* parasites in $g,1$ continue to support *avr* parasites, even though most of the parasite population is *AVR*. Hence the strength of selection for *avr* and against *AVR* is greater when A is higher (equation 8).

However, analysis of the elements of the Jacobian matrix shows that if $\eta > \gamma_1 > 0$ (i.e., if the benefit of IR is greater than its cost, as one would expect of inducible defenses) the effect of IR is to reduce the parameter range over which GFG polymorphism is stable. This happens in three ways.

First, direct FDS is reduced by increasing η . In equation 8, the right side becomes less negative. Biologically, when the frequency of *AVR* increases, the proportion of *RES* plants challenged by *AVR* parasites and thus expressing IR also increases.

TABLE 2. Fitnesses of hosts and parasites in model A with two parasite generations ($G = 2$)

	Parasite genotypes (frequencies) within host generation g			Fitness at beginning of host generation $g+1$	
	1st generation	Fitness of 1st parasite generation	2nd generation	Fitness of 2nd parasite generation	Host fitness
Host genotype	<i>AVR</i> (A_g)	0	<i>AVR</i> ($A_{g,1}$)	0	$(1-u)(1-\gamma_2)$
<i>RES</i> (R_g)	<i>avr</i> (a_g)	$1-b$	<i>avr</i> ($a_{g,1}$)	$(1-b)(1-\eta)$	$(1-u)(1-\varepsilon)(1-\gamma_1)$
			[<i>AVR</i> negligible]	—	—
Host genotype	<i>AVR</i> (A_g)	1	<i>avr</i> (a_g)	$1-b$	$(1-u)(1-\phi)$
			<i>AVR</i> ($A_{g,1}$)	1	$1-\phi$
<i>res</i> (r_g)	<i>avr</i> (a_g)	$1-b$	<i>avr</i> ($a_{g,1}$)	$1-b$	$1-\phi$
			<i>AVR</i> ($A_{g,1}$)	1	$1-\phi$
			<i>avr</i> ($a_{g,1}$)	$1-b$	$1-\phi$

Therefore, *avr* parasites infecting such *RES* plants have lower fitness when η is higher. This reduces direct FDS on *AVR* (equation 8).

Second, the proportions of *RES* plants that express IR once (cost γ_1) or twice (cost γ_2) increase with *AVR* frequency. *RES* plants are thus, less strongly selected by a high frequency of *AVR* when costs of inducing IR are high (equation 7). This increases the range of parameters over which *res* becomes fixed and polymorphism is not maintained.

Third, higher values of η diminish the mean fitness of *avr* pathogens, which means that selection against *AVR* parasites is weaker at higher values of η (equation 9).

Simulation results for $G > 2$. As coefficients of the Jacobian matrix could not be obtained analytically, we ran numerical simulations for $2 \leq G \leq 5$ (Fig. 1A to D). For $G \geq 3$, the recurrence equations for A_{g+1}/a_{g+1} and R_{g+1}/r_{g+1} become very cumbersome (Matlab code available on request for $2 < G < 6$), so an algorithm

to construct equations equivalent to equations 2 through 4 for $G > 2$ is described below.

(I) Up to generation $G - 1$, calculate parasite allele frequencies for the case with $G = 2$ as above, then for the third and subsequent generations (if $G > 3$) as below.

(II) New interactions in the G th parasite generation on *RES* plants are identified. (i) On those already infected by *avr* pathogens, the *avr* genotype persists (*avr* fitness is then $1 - b$). (ii) Newly produced *avr* pathogens can infect plants previously attacked unsuccessfully by *AVR* pathogens (*avr* fitness is then $1 - b$). (iii) Newly produced *AVR* strains can attack plants previously *AVR*-attacked (*AVR* fitness is then 0).

(III) New interactions in the G th parasite generation on *res* plants are identified. (i) Newly produced *avr* strains can outcompete an established *avr* or *AVR* strain (*avr* fitness is then $1 - b$). (ii) Newly produced *AVR* strains can outcompete an established *AVR* or *avr* strain (*AVR* fitness is then 1).

Fig. 1. Outcomes of gene-for-gene coevolution with polycyclic parasites over a range of numbers of parasite generations per host generation (G), in relation to the maximum cost to the plant of being diseased (ϕ) for $z = 1.4$ (equation 1). The model was run for two values of constitutive costs of plant resistance (u) and parasite virulence (b) with $u = b = 0.05$ (black lines) or 0.02 (gray lines). Solid and dashed lines are the upper and lower limits of ϕ , respectively, for coevolution to stable polymorphism. (i) When $\phi < u$ (below dotted lines), virulent parasites and resistant plants are eliminated. The loss of host fitness due to disease is smaller than the cost of resistance, so resistance alleles have a net cost. The loss of resistance results in a lack of selection for virulence. (ii) At intermediate values of ϕ , between the limits, there is long-term stable polymorphism, with the graph of allele frequencies spiraling towards an interior equilibrium point. (iii) At values of ϕ above an upper limit (solid lines), the graph of allele frequencies spirals away from the interior equilibrium point, so *avr* parasites and *RES* plants are fixed. The following parameters for induced resistance were used (γ , cost of IR; η , effectiveness of IR): **A**, No induced resistance ($\gamma = \eta = 0$); **B**, $\gamma = 0.05$ and $\eta = 0.2$; **C**, $\gamma = 0.05$ and $\eta = 0.5$; **D**, $\gamma = 0.1$ and $\eta = 0.5$.

(IV) Plant fitnesses are calculated by equation 1, setting G to be the number of generations of successful pathogen infection (by avr on RES plants and by AVR or avr on res).

Costs and benefits of IR are implemented as follows: (i) the cost of IR for the RES plant increases with the number (n) of successive AVR challenges and multiplies plant fitness by $(1 - \gamma)^n$ (16), and (ii) the effectiveness of IR increases with n and multiplies pathogen fitness by $(1 - \eta)^n$. In Figure 1, for each maximum number of parasite generations (G), n varies from 0 to G .

The stability of the equilibrium state was investigated by numerical simulations of host and parasite allele frequencies (46). Simulations were run with several values of ϕ ($0 \leq \phi \leq 1$) for 20,000 host generations, with various initial allele frequencies. The system was considered to be stable when the amplitude of the fluctuations of allele frequencies decreased in time and converged towards an equilibrium value for any of the initial allele frequencies tested (Fig. 1). The equilibrium point ($\hat{R}, \hat{a}$) was estimated as the average of frequencies over the last 1,000 generations. The system's behavior was then tested further by perturbing the allele frequencies in the vicinity of the equilibrium point, to check that frequencies would converge again to their stable values ($\hat{R}, \hat{a}$). If these criteria were not met, the system was considered to be unstable, in which case allele frequencies spiraled outwards towards the boundaries.

When ϕ is very high, RES alleles are strongly selected, increasing $\partial \Delta f_R / \partial f_A$, preventing stable polymorphism and causing RES (and thereafter avr) to become fixed (top of Fig. 1). As G increases, the system becomes stable over a broader range of ϕ (Fig. 1). The range of parameter values at which polymorphism is stable is wider with higher constitutive costs of RES and avr (comparing $u = b = 0.05$ with $u = b = 0.02$ in Fig. 1A without IR). This is consistent with predictions of previous models (4,30) that costs of RES and avr help to maintain polymorphism. However, changes in the parameter value of IR (γ and η) strongly modify the size of the stability area, limiting the effect of constitutive costs u and b on stability (Fig. 1). Comparison of different values of the cost of IR (γ) in Figure 1 indicates that increasing γ diminishes the stability area by increasing the value of ϕ required for polymorphism to persist (bottom limit of stability area in Fig. 1). At low ϕ ($\phi < u + (1 - \gamma)^G$), the cost of resistance outweighs its benefit so res and AVR alleles become fixed. Higher values of the effectiveness of IR (η) diminish the maximum value of ϕ for polymorphism to occur (top limit of stability area in Fig. 1), and thus reduce the size of the stability area. The reduction of the stability area because of increased η is more pronounced at higher G (compare $u = b = 0.05$ in Fig. 1B and D). With lower costs ($u = b = 0.02$), this effect is not clearly evident because the stability area is already small in Figure 1B.

Finite population (model B): Model description. In model B, results from infinite populations (model A) are extended to finite populations with variable host population size, assuming two parasite generations per host generation and auto-infection (46) (Table 1). Host population size depends on disease prevalence and disease severity. First, the stability of polymorphism is studied as a function of the auto-infection rate. Second, it is assumed that the cost of IR increases with enhanced competition among plants for resources (2,11,12,39). Following results from model A, the effect of population size on the cost of IR and therefore on polymorphism stability is then studied.

The epidemic process has two parts, based on the life cycle of biotrophic parasites such as rusts or mildews, in which GFG interactions are well known. First, overwintering spores from the previous host generation ($g - 1$) infect plants according to the rate of infection of the primary inoculum (ρ). Second, there is disease transmission from infected plants to healthy plants during the second parasite generation in a density-dependent manner. This allows an epidemic to build up during one host generation (47).

At the beginning of host generation g , there are R_g RES and r_g res plants in the population, while a_g and A_g are the numbers of

avr and AVR spores in the parasite population. After parasite generation $g,1$, X is the number of healthy plants (X_1 for RES or X_2 for res) and Y the number of infected plants, with Y_1 the number of RES infected by avr parasites, Y_2 res infected by avr and Y_3 res infected by AVR . Y_4 is the number of RES challenged by AVR parasites. For simplicity, we assume that ρ may limit infection but the number of parasite spores does not. The number of infected and noninfected plants is as follows at the start of $g,1$ (notation in Table 1):

$$X_1 = R_g(1 - \rho) \text{ and } X_2 = r_g(1 - \rho) \quad (10)$$

$$Y_1 = R_g \rho a_g / (A_g + a_g)$$

$$Y_2 = r_g \rho a_g / (A_g + a_g)$$

$$Y_3 = r_g \rho A_g / (A_g + a_g)$$

$$Y_4 = R_g \rho A_g / (A_g + a_g) \quad (11)$$

During the second parasite generation, disease transmission occurs from individual to individual depending on the density of infected plants, as assumed in other epidemiological models of animal and plant diseases (35,47). Moreover, we assume that only parasites that have infected plants in $g,1$ can produce infectious spores at $g,2$. We also define the following forces of infection for avr and AVR parasites (i.e., the rate at which a parasite genotype infects a new host):

$$h_a = (1 - b)\beta(Y_1 + Y_2) / N_g \text{ and } h_A = \beta Y_3 / N_g \quad (12)$$

where β is the probability of parasite transmission between plants, (i.e., the rate of secondary infection from plant to plant in the second parasite generation). We assume that the constitutive cost of avr (b) decreases spore production at $g,2$. N_g is the total number of plants (infected and uninfected) at host generation g (47):

$$N_g = R_g + r_g = X_1 + X_2 + Y_1 + Y_2 + Y_3 + Y_4$$

The following equations give the number of RES (R_{g+1} in equation 13) and res (r_{g+1} in equation 14) plants at host generation $g + 1$ (Table 3), where ψ is the auto-infection rate, the probability of a plant infected in $g,1$ remaining infected by the same parasite genotype in $g,2$ (3). IR parameters are similar to those in model A: γ_1 and γ_2 are the cost to the plant of expressing IR once and twice, respectively (with $\gamma_1 < \gamma_2$), and η is the effectiveness of IR in reducing parasite fitness. The fitness of infected plants is calculated following equation 1 in model A, where ε and ϕ are the costs of being diseased once and twice, respectively, and u is the constitutive cost of resistance. The number of RES and res plants at generation $g + 1$ are (Table 3)

$$R_{g+1} = \theta_g(1 - u) \left[\begin{aligned} &X_1[1 - h_a - h_A + h_A(1 - \gamma_1) + h_a(1 - \varepsilon)] + \\ &Y_4[h_a(1 - \varepsilon)(1 - \gamma_1) + h_A(1 - \gamma_2) + (1 - h_a - h_A)(1 - \gamma_1)] + \\ &\psi(1 - \phi)Y_1 + (1 - \psi)Y_1[h_a(1 - \phi) + (1 - \varepsilon)(h_A(1 - \gamma_1) + 1 - h_a - h_A)] \end{aligned} \right] \quad (13)$$

$$r_{g+1} = \theta_g \left[\begin{aligned} &X_2[1 - h_a - h_A + (h_a + h_A)(1 - \varepsilon)] + \\ &(Y_2 + Y_3)[\psi(1 - \phi) + (1 - \psi)((1 - \phi)(h_a + h_A) + (1 - \varepsilon)(1 - h_a - h_A))] \end{aligned} \right] \quad (14)$$

The following equations give the number of AVR spores (A_{g+1} in equation 15) and avr spores (a_{g+1} in equation 16) at host generation $g + 1$ (Table 3):

$$a_{g+1} = \delta_g(1 - d)(h_a(X_1 + X_2) + Y_4 h_a(1 - \eta) + \psi(Y_1 + Y_2) + (1 - \psi)h_a(Y_1 + Y_2 + Y_3)) \quad (15)$$

$$A_{g+1} = \delta_g(h_A X_2 + \psi Y_3 + (1 - \psi)h_A(Y_2 + Y_3)) \quad (16)$$

For example, during the second parasite generation, uninfected *res* plants (X_2) can either remain uninfected if they do not receive spores ($1 - h_a - h_A$) and have fitness 1, or be infected by *avr* (h_a) or *AVR* (h_A) parasites and have fitness $(1 - \varepsilon)$ (Table 3). Infected *res* plants can either (i) remain infected by auto-infection (ψ) and have fitness $(1 - \phi)$, (ii) be allo-infected ($1 - \psi$)($h_a + h_A$) and have fitness $(1 - \phi)$, or (iii) avoid re-infection by auto- or allo-infection ($1 - \psi$)($1 - h_a - h_A$), and have fitness $(1 - \varepsilon)$.

The plant population is regulated by a density-dependent rate of reproduction independent of parasite infection:

$$\theta_g = \frac{\theta_0}{1 + \zeta_H(R_g + r_g)} \quad (17)$$

where θ_g is the per capita production of seeds by uninfected plants (equations 13 and 14) (47), θ_0 is the maximum per capita production of seeds and ζ_H is a density dependence parameter. The maximum number of plants in the population is fixed to $N_{\max} = 1,000$, and $\theta_0 = 5$ (47) so that $\zeta_H = 0.004$.

The parasite population also has a density-dependent component, where the maximum number of spores in the population is set to the maximum number of plants $N_{\max} = 1,000$.

$$\delta_g = \frac{\delta_0}{1 + \zeta_P(a_g + A_g)} \quad (18)$$

δ_g is the per capita production of spores at the end of each host generation (equations 15 and 16) (47), δ_0 is the maximum per capita production of spores, and ζ_P is a density dependence parameter (similarly, $\zeta_P = 0.004$).

$N_{\max}$ is the maximum number of plants in a disease-free population, but in fact, the number of plants at equilibrium ($\hat{N}$) in a diseased population depends on the percentage of infected plants, the cost of being diseased, and the auto-infection rate. When equilibrium is reached in plant and pathogen population sizes, there is no variation in N . The seed production per capita at equilibrium ($\hat{\theta} = \theta_g = \theta_{g+1}$) can be approximated as

$$\hat{\theta} = 1 / (\rho(1 - \phi)(\psi + \beta(1 - \psi)) + \rho(1 - \varepsilon)((1 - \psi)(1 - \beta) - \beta) + \beta(1 - \varepsilon) + (1 - \rho)(1 - \beta))$$

Thus, $\hat{\theta} > 1$ if disease parameters are not zero ($\rho > 0$ or $\phi > 0$), and the plant population size at equilibrium is (equation 17):

$$\hat{N} = \frac{(\theta_0 - \hat{\theta})}{\zeta_H \hat{\theta}} \quad (19)$$

The plant population size at equilibrium diminishes when disease prevalence (higher values of ρ , β), disease severity (higher values of ϕ and ε), or the auto-infection rate (ψ) increase (equation 19).

Simulations. The stability of the polymorphic state depends on the auto-infection rate (46) and on costs of IR. Formal analysis of the finite population model is not feasible because the complexity and nonlinearity of the system does not allow analysis of the Jacobian matrix (47), so the evolution of plant and parasite populations was simulated for various values of ψ and ϕ . Simulations were conducted as described for model A, with different initial frequencies of alleles in plant and parasite populations. Initial numbers of plants and spores were low, with 50 plants and 25 parasite spores, so the initial disease prevalence was 0.5, and the host population was allowed to reach equilibrium ($\hat{N}$, equation 19). The influence of ψ on polymorphism stability is first shown for three different combinations of infection parameters: $\rho = \beta = 0.5$; $\rho = 0.5$ and $\beta = 0.8$; $\rho = \beta = 0.8$ (Fig. 2A), with fixed IR effectiveness ($\eta = 0.3$) and costs of IR ($\gamma_1 = 0.1$ and $\gamma_2 = 0.19$).

It was then assumed that to maintain a given value of IR effectiveness ($\eta = 0.3$), the cost of IR (γ_1 and γ_2) increased with enhanced competition for resources among plants (2,11,12,39). Competition was maximum when the plant population size N_g was equal to $N_{\max}$ with the cost of IR being $\gamma_1 = \gamma_{\max}$. The cost of expressing IR once was proportional to plant density:

$$\gamma_1 = \gamma_{\max} N_g / N_{\max} \quad (20)$$

For simplicity, and because of the lack of relevant published data, it was assumed that $\gamma_2 = 1 - (1 - \gamma_1)^2$ as in model A. Simulations were carried out here with $\gamma_{\max} = 0.1$ and for the three similar combinations of infection parameters as in Figure 2A ($\rho = \beta = 0.5$; $\rho = 0.5$ and $\beta = 0.8$; $\rho = \beta = 0.8$) (Fig. 2B).

TABLE 3. Fitness of hosts and parasites in model B with two parasite generations ($G = 2$) and auto-infection (rate = ψ)

	Parasite genotypes (frequencies) within host generation g			Fitness at beginning of host generation $g + 1$	
	1st generation	Auto-infection (ψ) Allo-infection ($1 - \psi$)	2nd generation	Fitness of 2nd parasite infection	Host fitness
Host genotype RES (R_g)					
X_1 noninfected plants		n/a ^a	No infection ($1 - h_a - h_A$)	n/a ^a	$1 - u$
			Challenged by AVR (h_A)	0	$(1 - u)(1 - \gamma_1)$
			Infected by avr (h_a)	$1 - b$	$(1 - u)(1 - \varepsilon)$
Challenged by AVR (Y_4)		n/a ^b	No infection ($1 - h_a - h_A$)	n/a ^a	$(1 - u)(1 - \gamma_1)$
			Challenged by AVR (h_A)	0	$(1 - u)(1 - \gamma_2)$
			Infected by avr (h_a)	$1 - b(1 - n)$	$(1 - u)(1 - \varepsilon)(1 - \gamma_1)$
Infected by avr (Y_1)	ψ $1 - \psi$ $1 - \psi$ $1 - \psi$	avr	$1 - b$	$(1 - u)(1 - \phi)$	
		Infected by avr (h_a)	$1 - b$	$(1 - u)(1 - \phi)$	
		Challenged by AVR (h_A)	0	$(1 - u)(1 - \varepsilon)(1 - \gamma_1)$	
		No infection	n/a ^a	$(1 - u)(1 - \varepsilon)$	
Host genotype res (r_g)					
X_2 noninfected plants		n/a ^a	No infection ($1 - h_a - h_A$)	n/a ^a	1
			Challenged by AVR (h_A)	1	$1 - \varepsilon$
			Infected by avr (h_a)	$1 - b$	$1 - \varepsilon$
Infected by AVR (Y_3)	ψ $1 - \psi$ $1 - \psi$ $1 - \psi$	AVR	1	$1 - \phi$	
		Infected by AVR (h_A)	1	$1 - \phi$	
		Infected by avr (h_a)	$1 - b$	$1 - \phi$	
		No infection ($1 - h_a - h_A$)	n/a ^a	$1 - \varepsilon$	
Infected by avr (Y_2)	ψ $1 - \psi$ $1 - \psi$ $1 - \psi$	avr	$1 - b$	$1 - \phi$	
		Infected by avr (h_a)	$1 - b$	$1 - \phi$	
		Infected by AVR (h_A)	1	$1 - \phi$	
		No infection ($1 - h_a - h_A$)	n/a ^a	$1 - \varepsilon$	

^a Not applicable: there is no infection as plants do not receive parasite spores.

^b Not applicable: there is no auto-infection because *AVR* parasites fail to infect *RES* plants.

Model B. Following results in Tellier and Brown (46), the parameter space in which polymorphism occurs is smaller at low ψ (Fig. 2A) because high ψ increases direct FDS for virulence in polycyclic parasites (46). Increasing the infection rates (ρ, β) enhances the proportion of infected plants (disease prevalence) and diminishes the number of plants at equilibrium (equation 20). Increasing the disease prevalence has two consequences (Fig. 2). First, the value of ϕ for which *res* and *AVR* are fixed diminishes (bottom line of each area in Fig. 2) because *RES* plants are eliminated if u is higher than the disease prevalence (function of ρ and β) multiplied by ϕ . Second, at intermediate to high ψ , the stability area increases with disease prevalence (upper limit of each area for stability in Fig. 2). This is because increasing disease prevalence enhances direct FDS.

When the cost of IR increases with higher plant density, the size of the parameter area for stability increases with higher dis-

ease prevalence (Fig. 2B). In fact, higher disease prevalence decreases plant density at equilibrium (equation 19), so for a fixed effectiveness of IR (η), the cost of IR is lower. Stable polymorphism then occurs at lower ϕ (bottom line of each area in Fig. 2B), because a lower cost of IR diminishes the disadvantage of *RES* against *res* alleles at low disease severity (equation 7). The effect of ψ on the size of the stability area is similar to that in Figure 2A.

DISCUSSION

Polymorphism in GFG interactions has often been explained by fitness costs of virulence in parasites and of resistance in plants (4,30,31,33). Recent theoretical work has shown, however, that while these costs are necessary, they are not sufficient to maintain stable, long-term polymorphism in single locus (14,46) or multi-locus GFG systems (41,47), because they do not create direct FDS (46). On the other hand, epidemiological and ecological factors can generate direct FDS. For example, polycyclic infection with a high rate of auto-infection allows maintenance of stable GFG polymorphism in both host and parasite (46). In this case, FDS operates by reducing the strength of selection for *avr* as that allele's frequency increases.

An important feature of plant disease in the natural world, which may be applicable to disease control in agriculture, is host-mediated interactions between parasites. Effective IR triggers systemic resistance via salicylic, jasmonate or ethylene signals in plants, and there is increasing evidence that IR is costly (2,13,21–23). For IR to evolve, its effectiveness against subsequent parasite attack should be greater than the cost of expressing those defenses, i.e., $\eta > \gamma$. For natural systems with coevolution between host and parasite, direct FDS occurs when parasites are polycyclic with auto-infection (model A) (46). Here, it is shown that increasing the effectiveness of IR reduces the strength of direct FDS ($\partial \Delta f_A / \partial f_A$) in the parasite population. Moreover, the stability of polymorphism also depends on the strength of indirect FDS (parasite gene frequencies affecting the strength of selection for host genes and vice-versa), and it is shown that increasing η and γ diminish the parameter space for which polymorphism in GFG interactions is stable. Increased effectiveness of IR increases selection against *avr* alleles by the host ($\partial \Delta f_A / \partial f_R$). On the other hand, a higher cost of IR enhances selection against *RES* alleles at low disease severity, thus decreasing $\partial \Delta f_R / \partial f_A$.

When more than two parasite generations per host generation are assumed ($G > 2$), without IR, the system is stable over a broader range of ϕ as G increases (Fig. 1A). This is because as G increases, *avr* parasites are favored, $\partial \Delta f_R / \partial f_A$ decreases and $\partial \Delta f_A / \partial f_R$ becomes larger, and direct FDS is more negative (46). By contrast, IR decreases the stability of polymorphism more strongly as G increases, because both the cost and the effectiveness of IR increase with the number of successive *AVR* challenges (16), reducing direct FDS on the parasite and increasing selection against *RES* plants at low ϕ (Fig. 1).

Cost of IR have been shown empirically to reach high values, up to 40% (2), and to be dependent on environmental resources (2,11,12,39). Competition among plants for limited resources (in light, nitrogen, or other nutrients) generally enhances the cost of inducing systemic resistance (2,13,12,39) but see Cipollini (11) for a counter-example. The number of plants in the population at equilibrium diminishes with increasing disease prevalence (depending on the primary and secondary infection rates ρ, β) and disease severity (ϕ). When the cost of IR depends on plant population size, therefore, polymorphism is more stable than in simulations in which the cost of IR is independent of the number of plants. This is because at higher disease prevalence, the plant population size at equilibrium becomes smaller, and thus competition among plants for resources is reduced. This tends to reduce the cost of IR necessary to maintain a fixed effectiveness of IR.

Fig. 2. Outcomes of gene-for-gene coevolution for polycyclic parasites in relation to the frequency of auto-infection (ψ) and the maximum cost to the plant being diseased (ϕ) for $z = 1.4$ (equation 1 in text), with constitutive costs of resistance (u) and virulence (b) of $u = b = 0.05$ (model B with finite plant population size $N_{\max} = 1000$). Here the effectiveness of induced resistance is $\eta = 0.3$. Simulations are shown for various values of infection parameters: $\rho = \beta = 0.5$ (black solid line); $\rho = 0.5$ and $\beta = 0.8$ (black dotted line); $\rho = \beta = 0.8$ (gray solid line). (i) When ϕ is small, virulent parasites and resistant plants are lost from the system (below a lower limit, i.e., the lower of each pair of lines). (ii) At intermediate values of ϕ , between the limits, there is long-term stable polymorphism, with the graph of allele frequencies spiraling towards the equilibrium point. (iii) At values of ϕ above an upper limit, the graph of allele frequencies spirals away from an interior equilibrium point, so *AVR* parasites and *res* plants are lost. **A**, The cost of IR is constant ($\gamma_1 = 0.1$) and **B**, the cost of IR is a linear function of the plant density (equation 20).

Our models only take into account direct costs to the plant, such as those due to systemic expression of defense proteins in response to the accumulation of chemical signals such as salicylic acid or jasmonic acid. These costs can be measured experimentally, for example by spraying plants with chemical inducers of defenses such as BION, methyl-jasmonate, or ethylene, and measuring plant seed production with or without IR in appropriate environmental conditions (2,13,21–23). However, costs of expressing IR may be more subtle and indirect (20,21). For example, antagonistic interactions have been found between SAR and ISR (19,26,40,45). This means that plants could express efficient SAR defenses against some parasites, such as fungi or viruses, but be more susceptible to other species such as herbivore insects. Furthermore, in a general ecological context, volatile compounds such as ethylene can attract herbivores (21,22). There are then two types of costs to a plant: the direct cost of defending itself and the indirect cost of being attacked by herbivores (21,22). Indirect costs may well be important in nature but are difficult to estimate and are beyond the scope of this study.

The models presented here are relevant to GFG coevolutionary interactions in natural pathosystems which exhibit GFG interactions (8,12,16,18,36,46), including ancestral natural populations of crops. They are not directly relevant to agricultural situations, in which several of the models' assumptions are not appropriate. For example, model B assumes that natural plant populations reach an equilibrium population which depends on resources available and parasite epidemics. This does not apply in agriculture because artificial fertilization and plant spacing reduce between-plant competition, and the plant population size does not depend on the previous year's seed production yield harvest but is fixed by farmers. It can be predicted, however, that polymorphism in GFG interactions in plants and parasites is more likely to occur in pathosystems in which the cost and effectiveness of IR are weak and in which disease is polycyclic and the pathogen has a high auto-infection rate. Data on auto-infection rates and IR are available in crop species and their parasite, but are lacking in natural species. For example, mildew and rusts show many GFG interactions (8,49) and are highly polycyclic (8,32,49) but, conforming the prediction, it appears that cultivated cereals lack the ability to express systemic IR (25). However, more experimental data are needed on variation in the cost of IR as a function of limited environmental resources and of the number of inductions.

Finally, it is notable the fact that constitutive costs of *RES* and *avr* alleles, which have been investigated in many crop and parasites species (5–7,15,29,48,51,53), increase the stability of polymorphism in GFG interactions (4,30,33,43). By contrast, inducible costs tend to drive the system toward instability, especially in highly polycyclic diseases, in which the cost of triggering IR increases with successive *AVR* challenges.

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