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EVOLUTION OF INCOMPATIBILITY-INDUCING MICROBES AND THEIR HOSTS

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Abstract.—In many insect species, males infected with microbes related to *Wolbachia pipientis* are "incompatible" with uninfected females. Crosses between infected males and uninfected females produce significantly fewer adult progeny than the other three possible crosses. The incompatibility-inducing microbes are usually maternally transmitted. Thus, incompatibility tends to confer a reproductive advantage on infected females in polymorphic populations, allowing these infections to spread. This paper analyzes selection on parasite and host genes that affect such incompatibility systems. Selection among parasite variants does not act directly on the level of incompatibility with uninfected females. In fact, selection favors rare parasite variants that increase the production of infected progeny by infected mothers, even if these variants reduce incompatibility with uninfected females. However, productivity-reducing parasites that cause partial incompatibility with hosts harboring alternative variants can be favored once they become sufficiently abundant locally. Thus, they may spread spatially by a process analogous to the spread of underdominant chromosome rearrangements. The dynamics of modifier alleles in the host are more difficult to predict, because such alleles will occur in both infected and uninfected individuals. Nevertheless, the relative fecundity of infected females compared to uninfected females, the efficiency of maternal transmission and the mutual compatibility of infected individuals all tend to increase under within-population selection on both host and parasite genes. In addition, selection on host genes favors increased compatibility between infected males and uninfected females. Although vertical transmission tends to harmonize host and parasite evolution, competition among parasite variants will tend to maintain incompatibility.

Key words.—Cytoplasmic incompatibility, *Drosophila simulans*, host-parasite coevolution, modifier evolution, *Wolbachia*.

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Many insects harbor microbes related to *Wolbachia pipientis* that affect embryo viability in crosses between strains (see, e.g., O'Neill et al. 1992; Stouthamer et al. 1993). "Unidirectional incompatibility" occurs when matings between infected males and uninfected females produce fewer viable progeny than the reciprocal cross or crosses within the infected or uninfected groups. As demonstrated theoretically (Caspari and Watson 1959) and empirically (Turelli and Hoffmann 1991), such infections, which are generally maternally transmitted (Hoffmann and Turelli 1988), tend to spread within and among populations. Although infected females may be less fecund (Hoffmann et al. 1990), they often have a net reproductive advantage in polymorphic populations, because they are generally compatible with infected males. This may suggest that selection among parasite variants favors greater incompatibility (Hurst 1991), but Prout (1994) has recently argued against this conjecture. A simple generalization of his analysis, presented below, shows that rare variants which increase the relative fecundity of parasitized females can spread, even if they increase the compatibility of infected males with uninfected females. I will examine more general models for the evolution of both parasite and host variants that affect cytoplasmic incompatibility (CI) to determine the directions in which incompatibility levels, maternal transmission rates, and fecundity losses may evolve.

The biology of unidirectional incompatibility has been most extensively investigated in *Drosophila simulans* (e.g., Hoffmann et al. 1986; Hoffmann et al. 1990; Nigro and Prout 1990; Montchamp-Moreau et al. 1991; Rousset et al. 1991; Turelli et al. 1992; Bressac and Rousset 1993). Hoffmann and his collaborators have described several differences in the behavior of this system in laboratory versus natural populations. The severity of incompatibility between infected males and uninfected females is generally greater in the laboratory than in nature. Infected females exhibit reduced fecundity in the laboratory but not in nature. Maternal transmission of the infection appears to be nearly perfect in the laboratory but is imperfect in nature. Conversely,

paternal transmission occurs occasionally in the laboratory but seems essentially absent in nature. All of these differences may be consequences of lower intracellular parasite densities (see Boyle et al. 1993; Breeuwer and Werren 1993a; Bressac and Rousset 1993) in nature, which probably result from environmental effects. However, similar variation in incompatibility levels, fecundity effects, and transmission rates may be controlled by genes in either the parasite or the host. No differences have yet been detected among *simulans* strains in their incompatibility response to a specific *Wolbachia* (Hoffmann and Turelli 1988); but Boyle et al. (1993) found dramatic interspecific differences, presumably caused by nuclear loci. When *Wolbachia* that produce high levels of incompatibility in *D. simulans* are transferred into *D. melanogaster,* they produce a low level of incompatibility, as seen in naturally infected *melanogaster* (Hoffmann 1988).

Wolbachia variants also affect CI. O'Neill et al. (1992) and Rousset et al. (1992) have shown that related forms of *Wolbachia* can produce different host compatibility types. Although all forms of the infection identified in *D. simulans* produce incompatibility between infected males and uninfected females, some variants are compatible with one another, but others are not (O'Neill and Karr 1990; Montchamp-Moreau et al. 1991). Maternally inherited "bidirectional incompatibility," with reduced egg hatch from both reciprocal crosses, has also been observed in *Culex* (Yen and Barr 1973) and *Nasonia* (Breeuwer and Werren 1990, 1993b). Similarly, selection among infected isofemale lines has been shown to reduce the level of incompatibility with uninfected lines (Hoffmann and Turelli 1988), and this reduction seemed to be maternally transmitted. These results show that both parasite and host genomes can affect CI, and the *D. simulans* laboratory/nature differences suggest how parameters may co-vary.

The models below consider how transmission rates, fecundity costs, and incompatibility levels may evolve under the control of either parasite or host genes. Motivated by the *D. simulans* results, the models assume that maternal transmission is imperfect, paternal transmission is absent, mating is random, and that the infection affects female fecundity but no other fitness component (Hoffmann et al. 1990). Discrete generations are assumed. These are all simplifying approximations. I also assume only vertical transmission. Although horizontal transmission must explain the discordant phylogenies of *Wolbachia* and their hosts in various insect orders (O'Neill et al. 1992; Rousset et al. 1992), it is very uncommon in nature, at least for *D. simulans.* For instance, in California *simulans* populations polymorphic for the infection, an earlier study (Turelli et al. 1992) found that all infected flies shared a common mtDNA restriction site variant, whereas the uninfected flies were polymorphic for this variant. Similarly, Hoffmann (1988, pers. comm.) found no infected *D. simulans* among more than 100 Australian isofemale lines; yet many sympatric populations of *D. melanogaster* showed high frequencies of infection. Because my interest centers on the direction of evolution rather than the maintenance of variation, I will further simplify the analysis of host evolution by assuming haploid genetics, which suffices to understand the fate of rare variants. For those uninterested in the derivations, each section begins with a brief description of the qualitative results.

Evolution of Parasite Variants

I first analyze selection on parasite variants, assuming that host properties are fixed. Prout (1994) argued that selection on the parasite does not usually favor higher levels of incompatibility. He assumed perfect maternal transmission and complete compatibility between parasite variants and concentrated on variants with extreme effects. (Prout called hosts carrying different microbe genotypes different "kinds of hosts," but his analysis concerns parasite, not host, genotypes.) I investigate parasite evolution more generally by considering variants that alter: (1) the fecundity of their female hosts, (2) the level of incompatibility between infected males and uninfected females, (3) the efficiency of maternal transmission, and (4) the reciprocal compatibility of infected hosts. Other possible consequences of these infections, including effects on viability, male virility, paternal transmission, horizontal transmission or assortative mating, can be investigated similarly.

For completely compatible parasite variants, two simple conclusions emerge: (1) selection favors variants that increase the number of infected progeny produced by infected females (i.e., the product of female fecundity and infection transmission efficiency), and (2) selection does not act directly on the level of incompatibility between infected males and uninfected females. When partial incompatibility between variants

TABLE 1. Glossary of notation.

Symbol	Usage
F	fecundity of infected females relative to uninfected females
H	hatch rate from incompatible fertilizations relative to compatible fertilizations
H_{12}	relative hatch rate from fertilizations of I_1 ova by I_2 sperm
I_0	uninfected host (also denoted U)
I_i	parasite of genotype i or infected host of genotype i
μ	fraction of uninfected ova produced by an infected female
p	frequency of infected hosts
p_i	frequency of hosts infected with parasite i or infected hosts of genotype i
q	frequency of uninfected hosts
q_i	frequency of uninfected host of genotype i
R_i	$p_i/(p_1 + p_2)$, fraction of infected hosts carrying I_i
s_f	$1 - F$
s_h	$1 - H$
U	uninfected host
U_i	uninfected host of genotype i

is allowed, more complex evolution is possible. Selection still favors variants that increase the number of infected progeny produced. However, rare variants that reduce compatibility with males carrying the prevailing infection can increase only if they cause a sufficiently large increase in the production of infected progeny. Variants that decrease the production of infected progeny will always be selected against when they are rare. However, they may spread once sufficiently common, if, for instance, the novel infected females are compatible with the alternative infected males, but the novel males are partially incompatible with the alternative infected females. Like underdominant chromosome rearrangements (Barton 1979; Lande 1985; Barton and Rouhani 1991), such variants may spread once established by chance in a local population. Although the level of incompatibility of infected males with uninfected females evolves only as a correlated response, plausible patterns of pleiotropy are likely to maintain incompatibility.

Completely Compatible Variants

I first treat unidirectional incompatibility, in which all infected hosts are completely compatible. Let I_1 and I_2 denote two completely compatible parasite variants (and the corresponding infected hosts). Thus, ova carrying I_i that are fertilized by sperm from I_j males ("I_j sperm") produce embryos that hatch at the same rate as embryos produced by ova and sperm from uninfected (U) individuals. For i = 1, 2, let H_i denote the relative hatch rate for embryos produced by incompatible fertilizations of U ova by I_i sperm (all other fertilizations are assumed to have relative hatch rate 1); and let F_i denote the fecundity of I_i females relative to U females. Set $H_i = 1 - s_{h_i}$ and $F_i = 1 - s_{f_i}$ for each i, with s_{h_i} and s_{f_i} nonnegative. (Table 1 provides a summary of notation.) I show below that under perfect maternal transmission, the frequency of I_1 among infected individuals will increase if and only if $F_1 > F_2$. Thus, with perfect maternal transmission and complete compatibility, selection acts to decrease the fertility costs of the infection (i.e., to increase the fecundity of infected females), irrespective of whether such variants decrease incompatibility.

Now consider incomplete maternal transmission (cf. Fine 1978), which occurs in natural *simulans* populations (Hoffmann et al. 1990; Turelli et al. 1992). Suppose that a fraction μ_i of the ova produced by I_i females are uninfected (U) and incompatible with I_1 and I_2 sperm. Let $p_{i,t}$ denote the frequency of I_i adults in generation t, and let $q_t = 1 - p_{1,t} - p_{2,t}$ denote the frequency of U adults. Table 2 translates the assumptions above into algebra, allowing for partial incompatibility between I_1 and I_2 (the new parameters H_{ij} are discussed below). Setting $H_{12} = H_{21} = 1$, $H_{01} = H_1$ and $H_{02} = H_2$, table 2 shows that the infection frequencies evolve according to

$$p_{i,t+1} = \frac{p_{i,t}F_i(1 - \mu_i)}{\bar{W}} \qquad \text{for i} = 1, 2, \tag{1}$$

with

$$\bar{W} = \bar{F} + (\bar{H} - 1)(p_1F_1\mu_1 + p_2F_2\mu_2 + q), \tag{2a}$$

$$\bar{F} = p_1F_1 + p_2F_2 + q, \qquad \text{and}$$

$$\bar{H} = p_1H_1 + p_2H_2 + q. \tag{2b}$$

Note that the average relative fecundity, $\bar{F}$, can be written as $1 - \bar{s}_f$ with $\bar{s}_f = p_1s_{f_1} + p_2s_{f_2}$, and the average relative hatch rate can be written as $\bar{H} = 1 - \bar{s}_h = 1 - (p_1s_{h_1} + p_2s_{h_2})$ (cf. Eq. [1] of Turelli et al. 1992). Equation (1) can be simply extended to any number of completely compatible infection types.

To understand the frequency dynamics of all three cytoplasmic forms (I_1, I_2, and U) with $\mu_i > 0$, it is useful to consider first the dynamics and equilibria with only one microbe type (cf. Cas-

TABLE 2. Derivation of recursions for frequencies of adult hosts carrying alternative parasite types, I_1 and I_2, allowing for bidirectional incompatibility. The frequency of I_i is denoted p_i for i = 1, 2; $q = 1 - p_1 - p_2$; $F_i = 1 - s_{f_i}$ = fecundity of I_i females relative to uninfected (U) females; $H_{ij} = 1 - s_{h_{ij}}$ = relative hatch rate from fertilizations of I_i ova by I_j sperm; μ_i = fraction of uninfected eggs produced by I_i females; and $\overline{W}$ is given by equation (7a) in the text.

Mating		Adult progeny × $\overline{W}$/Mating frequency		
♀ × ♂	Frequency	I_1	I_2	U
$I_1 \times I_1$	p_1^2	$F_1(1-\mu_1)$		$F_1\mu_1H_{01}$
$I_1 \times I_2$	p_1p_2	$F_1(1-\mu_1)H_{12}$		$F_1\mu_1H_{02}$
$I_1 \times U$	p_1q	$F_1(1-\mu_1)$		$F_1\mu_1$
$I_2 \times I_1$	p_1p_2		$F_2(1-\mu_2)H_{21}$	$F_2\mu_2H_{01}$
$I_2 \times I_2$	p_2^2		$F_2(1-\mu_2)$	$F_2\mu_2H_{02}$
$I_2 \times U$	p_2q		$F_2(1-\mu_2)$	$F_2\mu_2$
$U \times I_1$	p_1q			H_{01}
$U \times I_2$	p_2q			H_{02}
$U \times U$	q^2			1

pari and Watson 1959; Fine 1978; Hoffmann et al. 1990). Without interspecific horizontal transmission or immigration of infected individuals, absence of the infection (i.e., $p = 0$) is always a stable equilibrium. There will also be two feasible polymorphic equilibria, given by the roots of $\overline{W}(p) \equiv 1 - p(s_h + s_f) + p^2s_h(1 - F\mu) = F(1 - \mu)$, if

$$1 > s_h > \frac{s_f}{1 - 2\mu F} \tag{3a}$$

and

$$0 < \mu < \frac{1}{2}\left(1 - \sqrt{\frac{H(s_h - s_f^2)}{Fs_h}}\right), \tag{3b}$$

where $F = 1 - s_f$ and $H = 1 - s_h$. (In Hoffmann et al. [1990], I provided only the necessary condition [3a].) The higher equilibrium,

$$p_s = \left[s_f + s_h + \sqrt{(s_f + s_h)^2 - 4(s_f + \mu F)s_h(1 - \mu F)}\right] \div [2s_h(1 - \mu F)] > \tfrac{1}{2},$$

is stable. The lower equilibrium, p_u, obtained by changing the sign of the square root in (4), is unstable. (These equilibria become $p_s = 1$ and $p_u = s_f/s_h$ if $\mu = 0$.) The infection will be lost from an isolated population if its initial frequency is below p_u. Thus, sampling drift is required for the infection to become established locally. However, for a series of populations connected by migration, the infection can spread spatially if $p_u < 0.5$, once it becomes established in a "sufficiently large" local population (Turelli and Hoffmann 1991). This is analogous to the spread of underdominant chromosome rearrangements (Barton 1979; Lande 1985; Barton and Rouhani 1991). Assuming that (3a) and (3b) are satisfied, as μ increases, s_h decreases or s_f increases, the stable equilibrium, p_s, decreases and p_u increases until they coincide and both vanish, leaving only 0 as a stable equilibrium. For later reference, note that (3a) implies that when a stable polymorphism exists, $\overline{W}(p)$ is an increasing function near p_s.

The evolution of parasite variants can be understood by considering the frequency of I_i among infected individuals, $R_i = p_i/(p_1 + p_2)$, and ignoring $p = p_1 + p_2$, the fraction of the population that is infected. Equation (1) implies that

$$R_{i,t+1} = \frac{R_{i,t}(1 - \mu_i)F_i}{R_{1,t}(1 - \mu_1)F_1 + R_{2,t}(1 - \mu_2)F_2}. \tag{5}$$

This corresponds to haploid selection with fitnesses given by the "effective relative fecundities" $F_i(1 - \mu_i)$, the product of the relative fecundity of I_i females and their infection transmission efficiency. Thus, if several compatible variants co-occur, the variant with the highest $(1 - \mu_i)F_i$ will spread within the population of infected individuals, irrespective of whether infected individuals are increasing or decreasing in overall abundance.

It is plausible that as intracellular parasite densities increase, the fecundity of the infected females (F) falls, but transmission efficiencies ($1 - \mu$) rise. This would produce an inverse rela- + p_2, the frequency of uninfected individuals is

tionship between F_i and $1 - \mu_i$ across strains. If the biology of the microbe imposes such a constraint, equation (5) suggests that selection will favor intermediate values of F_i and $1 - \mu_i$ that increase $(1 - \mu_i)F_i$. The consequences of this evolution on p, the overall frequency of the infection, will depend on the pleiotropic effects of the variants on s_h, the severity of the incompatibility. Decreases in μ and increases in F increase p_s (see eq. 4), but this could be counteracted by pleiotropic decreases in s_h that decrease p_s.

This analysis assumes that uninfected ova produced by infected females are incompatible with sperm from infected males. As discussed in Turelli et al. (1992), an alternative explanation for the persistence of uninfected individuals in predominantly infected populations is that some infected larvae are "cured" during development (Stevens and Wicklow 1992). To model this, assume perfect maternal transmission of each infection ($\mu_i = 0$), and let μ_{c_i} denote the fraction of I_i larvae that are cured. Assuming that we census adults after curing, the dynamics of p_i are still described by equation (1) with μ_i replaced by μ_{c_i} and expression (2a) for $\overline{W}$ replaced by $\overline{W} = \bar{F} + (\bar{H} - 1)q$, with $\bar{F}$ and $\bar{H}$ as in (2b). Hence, the conditional frequencies of the infected types, R_i, evolve according to equation (5) with μ_i replaced by μ_{c_i}; and evolution acts to increase $(1 - \mu_{c_i})F_i$. The same qualitative result holds if both imperfect maternal transmission and curing are considered or if the uninfected ova from infected females remain compatible with sperm from infected males. For algebraic simplicity, these alternatives will not be considered further.

Partially Incompatible Parasites

Wolbachia variants can cause bidirectional incompatibility between infected *D. simulans*, such that both reciprocal F_1 crosses between infected strains exhibit reduced productivity (O'Neill and Karr 1990; Montchamp-Moreau et al. 1991; O'Neill et al. 1992; Rousset et al. 1992). Thus, it is of interest to let I_1 and I_2 be partially incompatible. The qualitative conclusion derived below is that a new variant which increases $F(1 - \mu)$, but makes females partially incompatible with infected males already present, will increase when rare only if the increase in "effective fecundity," $F(1 - \mu)$, is sufficiently large to offset the loss of progeny caused by partial incompatibility. Conversely, variants that decrease $F(1 - \mu)$ are always selected against when rare but may spread if they become locally common by chance. This process is analogous to the spread of a fecundity-reducing or imperfectly transmitted infection that causes unidirectional CI.

To simplify the notation, let I_0, instead of U, denote uninfected individuals. As before, assume that F_i, the fecundity of I_i females relative to uninfected females, satisfies $F_i \leq 1$. Let $\tilde{H}_{ij}$ denote the average hatch rate of embryos formed from I_i ova and I_j sperm. Assume that for all i, $\tilde{H}_{i0} = \tilde{H}_{ii} = \tilde{H}$, and set $H_{ij} = \tilde{H}_{ij}/\tilde{H}$. Finally, assume that $H_{ij} = 1 - s_{h_{ij}} \leq 1$ for all i and j.

From table 2, we see that the generalization of equation (1) is

$$p_{i,t+1} = \frac{p_{i,t}F_i(1 - \mu_i)\bar{H}_i}{\bar{W}} \qquad \text{for i} = 1, 2, \quad (6)$$

with

$$\bar{W} = p_1[F_1(1 - \mu_1)\bar{H}_1 + F_1\mu_1\bar{H}_0] + p_2[F_2(1 - \mu_2)\bar{H}_2 + F_2\mu_2\bar{H}_0] + q\bar{H}_0 \quad (7a)$$

and

$$\bar{H}_i = p_1H_{i1} + p_2H_{i2} + q. \quad (7b)$$

Hence, R_i, the frequency of I_i among infected hosts, changes according to equation (5) with $F_i(1 - \mu_i)$ replaced by the frequency-dependent fitness $F_i(1 - \mu_i)\bar{H}_i$. In this case, the R_i do not completely describe the dynamics; because the new effective relative fecundities, $F_i(1 - \mu_i)\bar{H}_i$, also depend on q, the frequency of uninfected individuals. Nevertheless, for all q, the net relative fecundities decrease (or remain constant) as the frequency of the competing infected type increases. Thus, the frequency dependence contributes to a disadvantage for rare types and does not promote coexistence. Indeed, Rousset et al. (1991) have shown that for any number of infected types with perfect maternal transmission ($\mu_i = 0$), no polymorphic equilibrium is stable under our assumptions.

This generalization of equation (5) implies that if I_2 is already present, I_1 will increase when rare within the population of infected individuals only if

$$F_1(1 - \mu_1)(1 - p_2s_{h_{12}}) > F_2(1 - \mu_2). \quad (8)$$

Hence, a variant that is partially incompatible with an existing type ($s_{h_{12}} > 0$) can increase among infecteds only if it increases $F(1 - \mu)$ enough to offset the reduction in egg hatch caused by incompatible fertilizations of I_1 ova by I_2 sperm.

Because of the negative frequency dependence, an unstable polymorphic equilibrium involving both incompatibility types may exist (Rousset et al. 1991). Thus, neither I_1 nor I_2 may be able to invade when it is rare and the other is near the stable equilibrium described by (4). However, as discussed below, this need not be an insurmountable barrier.

Recent analyses indicate that the severity of incompatibility is positively correlated with intrahost parasite density (Boyle et al. 1993; Breeuwer and Werren 1993a; Bressac and Rousset 1993). Thus, regulation of intrahost density may be an important process in parasite evolution. Suppose condition (8) is satisfied because I_1 has a higher relative fecundity, mediated by reduced parasite density. Then we also expect increased compatibility with uninfected individuals (i.e., $H_{01} > H_{02}$), but possibly some incompatibility with the more heavily infected I_2 (i.e., $s_{h_{12}} > 0$; Breeuwer and Werren 1993a). Conversely, if (8) is satisfied by reducing μ through an increase in parasite density, we expect $H_{01} < H_{02}$ and $s_{h_{12}} = 0$ (because ova from the more heavily infected I_1 would be expected to be "immune" to I_2 sperm). Without knowing the relationship between F and μ, it seems more probable that (8) would be satisfied by increases than decreases in density, because such variants would not be penalized by partial incompatibility with I_2 (i.e., $s_{h_{12}} = 0$), and they may have an advantage in intrahost competition.

Parasite variants that lower $F(1 - \mu)$ through increased intrahost density may also be able to spread by a process analogous to the spread of a fecundity-reducing CI microbe into an uninfected species. The generalization of equation (5) implies that I_1 will increase within the population of infected individuals whenever

$$F_1(1 - \mu_1)(1 - p_2 s_{h_{12}}) > F_2(1 - \mu_2)(1 - p_1 s_{h_{21}}). \quad (9a)$$

As discussed above, if I_1 produces a higher parasite density than I_2, we expect $s_{h_{12}} > 0$ and $s_{h_{12}} = 0$. With $s_{h_{12}} = 0$, (9a) implies that I_1 will increase in relative frequency if

$$p_1 > \frac{F_2(1 - \mu_2) - F_1(1 - \mu_1)}{s_{h_{12}} F_2(1 - \mu_2)}. \quad (9b)$$

The right-hand side of (9b) is analogous to the unstable equilibrium frequency for the infection discussed below equation (4); it will be feasible (i.e., between 0 and 1) only if $s_{h_{12}}$ is sufficiently large. A stochastic event would be necessary to push the frequency above this threshold. However, if the threshold is sufficiently low, the variant may be able to spread deterministically once it has become established in a local population. Thus, once partial incompatibility among parasite variants is considered, we see that parasite evolution will not inevitably lead to increasing $F(1 - \mu)$.

Host Control of Parasite Effects

Like cytoplasmic and nuclear genes (Clark 1984; Asmussen et al. 1987), infection status and nuclear genes behave as unlinked loci and so are strongly driven towards "linkage equilibrium;" that is, nuclear allele frequencies tend to rapidly become very similar within infected and uninfected individuals (Turelli et al. 1992). Thus, in partially infected populations, host alleles modifying CI parameters will generally occur in similar frequencies in both infected and uninfected cytoplasms. This makes their evolutionary fate more difficult to intuit than that of parasite variants, and it produces more complex criteria for the increase of rare pleiotropic alleles that affect several parameters. However, three basic messages emerge from the models below: (1) individual parameters tend to evolve in the same directions under both parasite or host control; (2) host selection tends to favor increased compatibility between infected males and uninfected females; and (3) once the parasite is established in a host population, selection does not favor host alleles that completely suppress it.

To simplify the notation required to understand the directions of parameter evolution, I assume that the host is a monoecious, sexual haploid, and consider two alternative host genotypes, A_1 and A_2. (Nevertheless, I will refer below to "males" and "females.") The invasion condition for a rare haploid variant A_1 is equivalent to that for a nonrecessive allele in diploids (haploid A_2 plays the role of the homozygote A_2A_2, and haploid A_1 plays the role of the invading heterozygote A_1A_2); thus, this simplification should not restrict the generality of the results. Following random mating and fertilization, diploid zygotes split into haploid adults. I assume that only one form of the incompatibility-causing microbe is present and denote infected individuals of genotype A_i by I_i and uninfected A_i individuals by U_i. Let p_i (q_i) denote the frequency of adult I_i (U_i). The frequency of infected individuals in the population is $p = p_1$

$q = 1 - p$, and the frequency of allele A_1 is $p_{A_1} = p_1 + q_1$. In principle, host alleles can modify either the properties of infected individuals or the susceptibility of uninfected ova to sperm from infected males. For simplicity, these two sorts of modifiers will be considered separately.

Host Alleles That Do Not Affect the Susceptibility of Uninfected Ova

Such variants alter only the parasite's effects on infected individuals. Let $F_i \leq 1$ denote the fecundity of I_i females relative to uninfected females, and let μ_i denote the fraction of uninfected ova produced by I_i. Because both genotypes of uninfected ova, U_1 and U_2, are assumed to be equivalent, denote them by I_0. As before, assume that the relative hatch rate of embryos produced by I_i ova and I_j sperm is H_{ij}, with $H_{i0} = H_{jj} = 1$ for i, j = 0, 1, 2, and $H_{ij} = 1 - s_{h_{ij}} \leq 1$ for all i and j.

To derive the frequency recursions, the logic of table 2 must be extended slightly to consider 16 types of matings and Mendelian segregation. For instance, matings between I_1 females and I_2 males occur with frequency p_1p_2. With incomplete maternal transmission, such matings produce all four types of progeny. Their contributions to I_1, I_2, U_1 and U_2 in the next generation are proportional to $F_1(1 - \mu_1)H_{12}/2$, $F_1(1 - \mu_1)H_{12}/2$, $F_1\mu_1H_{02}/2$, and $F_1\mu_1H_{02}/2$, respectively. The dynamics of this system are analogous to those produced by mutation and frequency-dependent selection acting on two unlinked loci in a sexual haploid (e.g., Bulmer 1989). We will avoid as much of the algebraic complexity as possible by concentrating on conditions for a new variant to increase when rare. Letting p_i' and q_i' denote the frequencies in the next generation, we have

$$\begin{aligned}\bar{W}p_1' &= p_1F_1(1 - \mu_1) \\ &\quad - \tfrac{1}{2}[p_1p_{A_2}F_1(1 - \mu_1) - p_2p_{A_1}F_2(1 - \mu_2)] \\ &\quad - \tfrac{1}{2}p_1p_2[F_1(1 - \mu_1)s_{h_{12}} \\ &\qquad + F_2(1 - \mu_2)s_{h_{21}}] \qquad (10a)\end{aligned}$$

and

$$\begin{aligned}\bar{W}q_1' &= (q_1 + p_1F_1\mu_1)\bar{H}_0 \\ &\quad + \tfrac{1}{2}p_1p_2(F_2\mu_2H_{01} - F_1\mu_1H_{02}) \\ &\quad + \tfrac{1}{2}(p_2q_1F_2\mu_2 - p_1q_2F_1\mu_1) \\ &\quad + \tfrac{1}{2}(p_1q_2H_{01} - p_2q_1H_{02}), \qquad (10b)\end{aligned}$$

with

$$\begin{aligned}\bar{W} &= p_1[F_1(1 - \mu_1)\bar{H}_1 + F_1\mu_1\bar{H}_0] \\ &\quad + p_2[F_2(1 - \mu_2)\bar{H}_2 + F_2\mu_2\bar{H}_0] + q\bar{H}_0 \qquad (11a)\end{aligned}$$

and

$$\bar{H}_i = p_1H_{i1} + p_2H_{i2} + q, \qquad (11b)$$

as in (7). The analogous recursions for p_2' and q_2' are obtained by interchanging 1s and 2s in (10).

A complete analysis of the dynamics requires following three variables, for instance, p_{A_1}, p, and the "cytonuclear disequilibrium" parameter, $D = p_1q_2 - p_2q_1$ (Clark 1984; Asmussen et al. 1987). The details of the invasion analysis are presented in the Appendix. Here I concentrate on the qualitative results. First consider variants that alter only one parameter. A combination of analytical and numerical analyses shows that selection on rare host variants tends to increase F and decrease μ, just as it does for rare parasite variants. Similarly, selection acts against rare host alleles A_1 producing infected ova that are partially incompatible with sperm from infected males carrying A_2 (i.e., $s_{h_{12}} > 0$), just as for rare parasite variants (cf. condition 8). However, new forces of direct selection appear on host variants, associated with the fact that they occur in both infected and uninfected cytoplasms. For instance, rare variants A_1 that produce partial incompatibility between I_1 sperm and I_2 ova (i.e., $s_{h_{21}} > 0$) will also be selected against. Moreover, in contrast to the case of parasite variants, there is direct selection on host variants to increase the compatibility of infected males with uninfected females; that is, if allele A_1 changes only H_{0i}, it increases when rare if and only if $H_{01} > H_{02}$. Hence, direct selection favors increases in F, $1 - \mu$, and H_{0i}; and it acts against partial incompatibility between infected forms. Because of the simple directional selection on F, $1 - \mu$, and H_{0i}, the conditions for increase of rare variants correspond to the conditions for their fixation when common. Thus, the same qualitative predictions should emerge from a complete diploid analysis as long as heterozygotes have intermediate parameter values. As with parasite variants, rare alleles that lead to partial incompatibility be-

tween I_1 and I_2 have a frequency-dependent disadvantage. As discussed above, such alleles may be able to spread once they become established locally by stochastic events that push them past the unstable equilibrium.

Because host selection acts to increase compatibility with uninfected ova, and this parameter does not directly affect the relative fitness of parasite variants (see invasion criterion 8), parasites that have a longer history of association with a particular host may produce lower levels of incompatibility. The same prediction emerges below from an analysis of host variants that alter the susceptibility of uninfected ova to sperm from infected males. However, such selection can occur only if imperfect maternal transmission, or some equivalent factor, maintains uninfected individuals in the population.

Conclusions about the directions of evolution of individual parameters are tentative, because they do not take into account the likely relationships among the parameters. Unfortunately, I can find no simple combination of parameters analogous to (8) that determines the fate of rare alleles that alter several parameters (i.e., pleiotropic modifiers). The full expression that emerges from the invasion analysis in the Appendix seems uninformative. A useful, but not infallible, guide to the fate of pleiotropic modifiers can be obtained by ignoring linkage disequilibrium and seeking conditions for p_{A1} to increase when it is near zero. The resulting heuristic condition is

$$[F_1(1-\mu_1) - F_2(1-\mu_2)] + [(pH_{02} + q)(F_1\mu_1 - F_2\mu_2)] + [(pF_2\mu_2 + q)(H_{01} - H_{02})] - p[F_1(1-\mu_1)s_{h_{12}} + F_2(1-\mu_2)s_{h_{21}}] > 0. \quad (12)$$

Although counterexamples to this condition can be easily found (see below), it correctly predicts how modifiers affecting only individual terms will evolve. Moreover, numerical results described in the Appendix suggest that variants satisfying (12) will very often satisfy the exact invasion conditions. Each of the four terms in square brackets in (12) describes a different aspect of selection on modifier alleles. The first implies that selection favors host genotypes that increase the number of infected offspring produced by infected females $[F_1(1-\mu_1) > F_2(1-\mu_2)]$. This is the selection criterion that arose from considering compatible parasite variants (cf. eq. 5). The second term suggests a contradictory criterion: selection favors increasing the number of uninfected offspring from infected females ($F_1\mu_1 > F_2\mu_2$). However, this term is likely to be smaller than the first, because it is proportional to the average hatch rate for uninfected ova ($pH_{02} + q$) and the rate at which maternal transmission fails (the μ_i). The third term in (12) implies that selection favors higher levels of compatibility with uninfected ova ($H_{01} > H_{02}$). As expected, this term is proportional to the frequency of uninfected individuals in the population. Finally, the fourth term implies selection against incompatibility between the infected resident I_2 and either the invading infected males ($s_{h_{12}} > 0$) or females ($s_{h_{21}} > 0$). A variant producing partial incompatibility between infected individuals will spread locally only if it produces a sufficiently large increase in effective fecundity or compatibility with uninfected individuals.

Numerical Example

A numerical example will illustrate the accuracy of the heuristic condition (12) and the different time scales likely to apply to the evolution of the incompatibility parameters versus the population dynamics of overall infection frequencies. Suppose that $H_{02} = 0.55$, $F_2 = 0.95$ and $\mu_2 = 0.04$. These values are consistent with data from natural populations of *D. simulans* and produce a stable polymorphic infection frequency at $p = 0.938$ (Turelli et al. 1992). (The corresponding unstable equilibrium is $p_u = 0.217$.) Consider a variant that increases compatibility with uninfected flies, increases fecundity, but decreases the efficiency of maternal transmission (e.g., $H_{01} = 0.65$, $F_1 = 0.98$, and $\mu_1 = 0.06$). According to (12), such a variant will increase when rare only when

$$0.036 > s_{h_{12}} + 0.990\, s_{h_{21}}; \quad (13a)$$

but the exact invasion analysis (Appendix) implies that such a variant will increase if and only if

$$0.029 > s_{h_{12}} + 0.990\, s_{h_{21}}. \quad (13b)$$

This shows that weak incompatibility between the infected flies of different genotypes suffices to prevent the spread of such a variant when rare.

Figure 1 shows the dynamics of the allele frequency, infection frequency, and disequilibrium if $s_{h_{12}} = s_{h_{21}} = 0$, with initial conditions $p = 0.22$ or $p = 0.938$, $p_{A_1} = 0.01$, and $D = 0$. In this case, the one-dimensional analysis leading to criterion (12) implies that for $p_{A_1} \cong 0$, $p'_{A_1}/p_{A_1} \cong 1.016$,

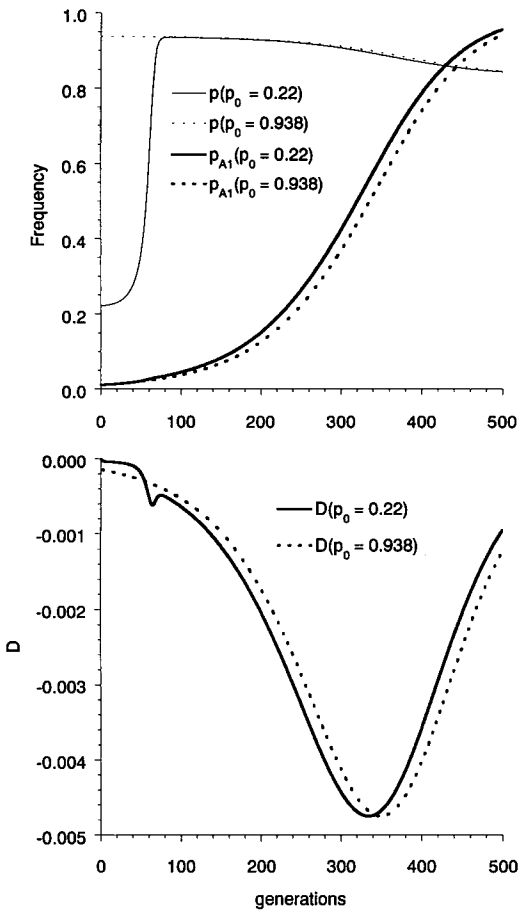

FIG. 1. The upper figure shows trajectories for the infection frequency, p, and the frequency of the modifier allele A_1, p_{A_1}; the lower figure displays the corresponding disequilibrium coefficient, $D = p_1q_2 - p_2q_1$. In each figure, the solid lines were produced with an initial infection frequency of $p_0 = 0.22$, and the dotted lines were produced with $p_0 = 0.938$. For all trajectories, $D = 0$ and $p_{A_1} = 0.01$ initially, $H_{01} = 0.65$, $F_1 = 0.98$, $\mu_1 = 0.06$, $s_{h_{12}} = s_{h_{21}} = 0$, $H_{02} = 0.55$, $F_2 = 0.95$, and $\mu_2 = 0.04$.

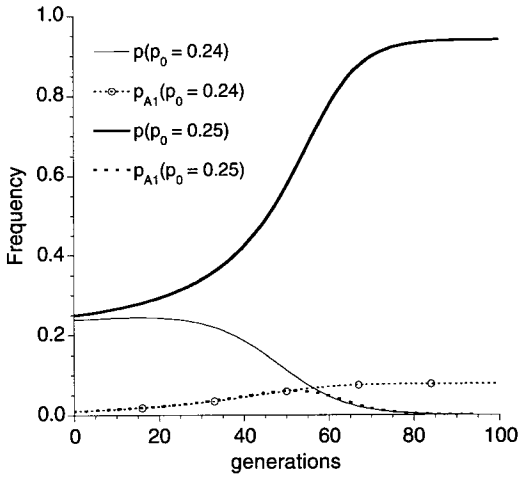

FIG. 2. Trajectories for the infection frequency, p, and the frequency of the modifier allele A_1, p_{A_1}, for two different initial infection frequencies, $p_0 = 0.24$, and $p_0 = 0.25$. For both sets of trajectories, $D = 0$ and $p_{A_1} = 0.01$ initially, $H_{01} = H_{21} = 1$, $F_1 = 1$, $\mu_1 = 1$, $H_{02} = H_{12} = 0.55$, $F_2 = 0.95$, and $\mu_2 = 0.04$.

whereas the complete three-dimensional analysis implies that the stability-determining eigenvalue is 1.013. The time scale for the evolution of modifiers of this magnitude is hundreds of generations, an order of magnitude longer than the time scale of the infection's spread through a population. For California *D. simulans* populations with roughly 15 generations per year (Turelli and Hoffmann 1991), this evolutionary time scale corresponds to decades. Because the infection frequency changes so rapidly relative to the dynamics of the modifier allele, the behavior of the modifier allele (and D) is essentially independent of the initial infection frequency (fig. 1).

"Suppressor" Mutations.—One type of extreme host variant is of particular interest. Consider an allele, A_1, that completely suppresses the growth of the parasite. Infected individuals of this genotype would be equivalent to uninfected individuals, so that $\mu_1 = 1$, $F_1 = 1$, $H_{01} = H_{21} = 1$, and $H_{12} = H_{02} = 1 - s_{h_{02}} < 1$. In this case, both the heuristic condition (12) and the exact invasion analysis predict that such a variant can increase when rare in a population at a stable polymorphism for the infection (i.e., $p = p_s$ from eq. 4) only if

$$-[2s_{h_{02}}p(1 - F_2\mu_2) - (s_{f_2} + s_{h_{02}})] > 0. \quad (14)$$

The term in square brackets on the left-hand side of (14) is the derivative of $\overline{W}$ with respect to p, when the population is monomorphic for A_2. As noted previously, this derivative is positive at p_s; hence, suppressors can never increase within populations at a stable infection frequency equilibrium. At low infection frequencies, however, such variants can be favored.

This example is informative because these variants produce large changes in the parameters and might be expected to display the fastest allele frequency dynamics. Nevertheless, for parameter values comparable to those observed in *D. simulans*, the dynamics of such modifiers are still

much slower than the infection frequency dynamics. This is illustrated for two initial infection frequencies in figure 2. If the initial infection frequency is too low, the infection is lost from the population, and the modifier reaches only a moderate frequency before the infection-induced selection vanishes. If the initial infection frequency is slightly higher, the suppressor allele increases initially but is then driven to zero as the infection spreads.

Host Alleles That Affect Only the Susceptibility of Uninfected Ova

Finally, consider host variants that alter the susceptibility of infected ova to sperm from infected males, but leave unchanged the properties of infected individuals. Thus, both infected genotypes are equivalent and fully compatible. Denote the relative fecundity of the infected individuals by $F \leq 1$ and their maternal transmission efficiency by $1 - \mu$. The only relative hatch rates that may be less than one are those of embryos produced from U_i ova and I sperm, denote these by $H_i = 1 - s_{h_i}$. The equations analogous to (10) are

$$\overline{W} p'_1 = p_1 F(1 - \mu) - \tfrac{1}{2} F(1 - \mu)(p_1 p_{A_2} - p_2 p_{A_1}) \quad (15a)$$

and

$$\overline{W} q'_1 = (q_1 + p_1 F\mu)(pH_1 + q) + \tfrac{1}{2} p_1 p_2 F\mu(H_2 - H_1) + \tfrac{1}{2} F\mu(p_2 q_1 - p_1 q_2) + \tfrac{1}{2}(p_1 q_2 H_2 - p_2 q_1 H_1), \quad (15b)$$

with

$$\overline{W} = pF + q - p[s_{h_1}(q_1 + p_1 F\mu) + s_{h_2}(q_2 + p_2 F\mu)]. \quad (16)$$

The exact invasion analysis described in the Appendix shows that A_1 can increase when rare if and only if

$$H_1 > H_2, \quad (17)$$

Not surprisingly, uninfected females from polymorphic populations are expected to evolve resistance to incompatibility.

Discussion

Intuition may suggest that CI-causing microbes are "selfish" parasites that should evolve ever-higher levels of incompatibility, but Prout (1994) showed that simple models do not support this conjecture. Although the spread of the parasite requires cytoplasmic incompatibility, the level of incompatibility between infected males and uninfected females evolves under parasite control only as a correlated response to direct selection on the fecundity of infected females, efficiency of maternal transmission of the infection and levels of compatibility between parasite variants. For variants that are completely compatible, we expect selection to increase the composite parameter $F(1 - \mu)$ (see eq. 5), which is the number of infected progeny produced by infected females. The appearance of the infected host's relative fecundity in this fitness criterion reflects the evolutionary coupling imposed by vertical transmission. This is consistent with previous theoretical discussions (Anderson and May 1982; Ewald 1987; Bull and Rice 1991) and empirical analyses (Bull et al. 1991; Bull and Molineux 1992; Herre 1993) of vertically transmitted parasites. Because relative fecundity, F, is expected to decrease with intrahost parasite density, and maternal transmission efficiency, $1 - \mu$, is likely to increase, their product should be maximized at intermediate parasite densities. Similarly, models for the evolution of horizontally transmitted parasites suggest that fitness is maximized for intermediate levels of virulence, if transmission rates are inversely correlated with virulence (May and Anderson 1990; Antia et al. 1994). The parasite's reproduction is simply more tightly coupled to that of its host under vertical transmission.

The simple maximization principle that governs the evolution of completely compatible parasite variants can be violated once partial bidirectional incompatibility between variants is considered. If parasite variants are partially incompatible, a new variant will increase when rare only if it increases the "effective fecundity" of infected females enough to offset the progeny it loses through incompatibility with the infected males already present (see condition 8). Thus, it may be easier for evolution to increase than decrease parasite densities. Selection for "resistance" to alternative CI-inducing parasites is likely to preserve incompatibility with uninfected forms as a by-product. If increasing intracellular density evolves in response to this com-

petition, increasing levels of incompatibility may result. However, this trend will ultimately be halted by fecundity losses for the host (and parasite). The connections between incompatibility levels, fecundity costs and transmission efficiencies are likely to vary across taxa, leading to different levels of incompatibility. Variation in these patterns of pleiotropy may underlie the great variation in levels of unidirectional incompatibility associated with *Wolbachia* in different taxa: from complete (e.g., *Tribolium*; Wade and Stevens 1985) to nearly undetectable (e.g., *D. melanogaster*; Hoffmann 1988).

Although only parasite variants that increase $F(1 - \mu)$ will tend to increase when rare in an isolated population, we know that imperfectly transmitted parasites that cause CI have spread in nature, despite tending to be eliminated when rare. Thus, some variants that decrease $F(1 - \mu)$ may also be able to spread, if they are favored once they become sufficiently common (see 9a). This will occur only if the parasite variants exhibit partial incompatibility with each other; in particular, the male carriers of the novel form must be partially incompatible with females carrying an already present variant. If the novel variants become sufficiently common by chance, the "cost" of reduced $F(1 - \mu)$ can be offset by the "benefit" of partially sterilizing females with the alternative infection. This process of deterministic spread following a stochastic movement past an unstable equilibrium has been discussed extensively for underdominant chromosome rearrangements (Barton 1979; Lande 1985; Barton and Rouhani 1991). For CI-inducing parasites, it provides a mechanism whereby decreases in $F(1 - \mu)$ may evolve.

The analogy with chromosome rearrangements may help clarify the spatial distribution of bidirectionally incompatible infected forms in various taxa, especially *Culex pipiens* (Rousset et al. 1991). As shown by Barton (1979), "waves of advance" associated with unstable equilibria can be "trapped" by regions of relatively low dispersal. Hence, as argued by Barton and Hewitt (1989), many hybrid zones may be "tension zones" in which migration maintains two forms that would not coexist without spatial subdivision. Similarly, bidirectionally incompatible variants of *Wolbachia* may tend to coexist in tension zones defined by barriers to dispersal. In particular, some locally successful variants that decrease $F(1 - \mu)$ may get trapped in peripheral populations from which they cannot spread.

The actual directions of parasite evolution can be studied by measuring the fecundity, transmission and incompatibility parameters for different *Wolbachia* in *D. simulans* (or other taxa), determining their phylogenetic relationships, and quantifying the intracellular *Wolbachia* densities they produce. This can be approached either with the *Wolbachia* variants that occur naturally in *D. simulans* or with forms that can be transferred reciprocally between the species by microinjection (Boyle et al. 1993) or backcrossing (Breeuwer and Werren 1993b). A phylogenetic trend toward decreasing $F(1 - \mu)$ would indicate that population subdivision is playing a central role in the evolution of this host-parasite interaction. Conversely, if $F(1 - \mu)$ tends to increase, this would suggest that the within-population "increase when rare" criterion dominates. By introducing a novel *Wolbachia* into a large laboratory population, the prediction that $F(1 - \mu)$ should increase might be tested directly.

Although incompatibility with uninfected forms evolves only via pleiotropy under simple models of parasite evolution, direct selection on host variants favors decreased susceptibility of uninfected ova to incompatibility (see criteria 12 and 17). Thus, we expect populations that have been polymorphic for the infection for long periods to exhibit less severe incompatibility than populations that have not been exposed to the incompatibility-inducing microbes; and this effect is likely to be mediated by host genes. This prediction can be tested in *D. simulans* by comparing the incompatibility between infected Riverside males and uninfected females from southern California versus Australia. *Wolbachia* has been prevalent in Riverside *simulans* since at least 1984 (Hoffmann et al. 1986), but has only recently been found in Australian *simulans*. Despite the high frequency of infected flies in the Riverside population, uninfected flies are continually being introduced by imperfect female transmission and/or "curing" of larvae; and selection should reduce their susceptibility. Selection on rare host variants that affect infected individuals is more complex (see inequality 12). However, such selection should also lead to increased compatibility with uninfected ova, decreased fecundity deficits for infected females, and increased efficiency of maternal transmission. Ignoring variants that can only increase when sufficiently common, we expect the lowest values of $F(1 - \mu)$ in recently parasitized host populations. Increased knowledge of CI in various taxa—es-

pecially understanding the mechanistic bases for incompatibility and the covariation of transmission, fecundity and incompatibility parameters across strains and conditions—will permit more detailed evolutionary analyses.

CI-inducing microbes may contribute to reproductive isolation between species (Breeuwer and Werren 1990). However, because selection acts against rare microbe variants that are partially incompatible with forms already present (condition 8), bidirectional incompatibility is most likely to arise from secondary contact between forms that diverged in allopatry. When bidirectionally incompatible variants come into contact, all but one tends to be eliminated (Rousset et al. 1991). However, selection can act to modify their incompatibility in "tension zones" where continued migration insures coexistence. A preliminary two-population analysis suggests that in such cases, selection tends to diminish rather than reinforce reproductive isolation (unpublished results). Thus, although CI may contribute to reproductive isolation between taxa, this is more likely to arise as a byproduct of host-parasite coevolution, than as a direct product of natural selection.

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Appendix

The complete description of the dynamics of equations (10) or (15) requires following three variables, such as p_{A_1}, p, and $D = p_1q_2 - p_2q_1$. Here I derive the conditions for a rare variant A_1 to increase and discuss some numerical results. I concentrate on the more complex situation in which the modifier allele A_1 affects the parameters for infected individuals.

Let p_s denote the stable equilibrium allele frequency for the infection when the population is monomorphic for A_2 (cf. eq.4). Allele A_1 invades if and only if the three-dimensional equilibrium point $(p_{A_1}, D, p) = (0, 0, p_s)$ is unstable. Denote the recursions for these variables by

$$p'_{A_1} = f_1(p_{A_1}, D, p), \tag{A1a}$$

$$D' = f_2(p_{A_1}, D, p), \tag{A1b}$$

and

$$p' = f_3(p_{A_1}, D, p). \tag{A1c}$$

The local stability of $(0, 0, p_s)$ is determined by the magnitude of the largest eigenvalue of the 3×3 Jacobian matrix $\mathbf{A} = (a_{ij})$, where

$$a_{i1} = \frac{\partial f_i(0, 0, p_s)}{\partial p_{A_1}}, \qquad a_{i2} = \frac{\partial f_i(0, 0, p_s)}{\partial D},$$

and

$$a_{i3} = \frac{\partial f_i(0, 0, p_s)}{\partial p} \qquad \text{for } i = 1, 2, 3. \tag{A2}$$

Note that a_{11} is the linearized rate of increase of p_{A_1} at $D = 0$. The criterion used to obtain the heuristic condition (12) for A_1 to spread is just

$$a_{11} > 1. \tag{A3}$$

The exact conditions can be reduced to an analysis of the eigenvalues of a 2×2 matrix. To see this, first note that $a_{13} = a_{23} = 0$. This can be easily shown by using a symbolic manipulation program such as Mathematica (Wolfram 1991). Thus, one of the three eigenvalues of $\mathbf{A}$ is $a_{33} = \partial f_3(0, 0, p_s)/\partial p$; but this term determines the stability of the one-dimensional infection dynamics, in the absence of genetic variation. Thus, $|a_{33}| < 1$ follows from the assumption that p_s is a stable equilibrium for this one-dimensional system; and the stability of $(p_{A_1}, D, p) = (0, 0, p_s)$ is governed by the larger eigenvalue of the 2×2 matrix obtained by deleting the third row and column of $\mathbf{A}$.

Next note that if A_1 doesn't change the parameter values at all, $a_{21} = 0$, $a_{11} = 1$ (corresponding to neutral dynamics for equivalent alleles), and a_{22} describes the rate of decay of disequilibrium. For realistic parameter values, we expect the eigenvalues of the stability-determining matrix,

$$\mathbf{B} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, \tag{A4}$$

to be real and positive. This is easily proven for modifier alleles that produce only small changes in the parameters. Conditions for the dominant eigenvalue of $\mathbf{B}$ to be greater than 1 can be obtained from the Schur-Cohn criterion (May 1974, pp. 219–220). This implies

that when a_{11} and a_{22} are both positive, a necessary and sufficient condition for the larger eigenvalue of **B** to exceed 1 is

$$(a_{11} - 1)(1 - a_{22}) + a_{12}a_{21} > 0. \qquad \text{(A5)}$$

This is the exact invasion criterion applied to host variants.

For variants that alter only one parameter, (A5) simplifies dramatically. For host variants that affect only H_{0i}, (A5) reduces to $H_{01} > H_{02}$. The same condition emerges for host variants that affect only uninfected individuals (see 17). For variants that affect other parameters, I was unable to simplify the algebra without some restrictions on the parameter values. For instance, if $s_{h_{12}} > 0$ or $s_{h_{21}} > 0$ and all other parameters are unchanged, I can show that (A5) is never satisfied under the weak constraint that $\mu < 1/3$ (cf. 3b). For variants that alter only μ or F, (A5) remains messy, but simplifies considerably if only small changes in these parameters are considered (so that products of differences can be ignored). In these cases, I can show that under the mild constraint $F_2(1 - \mu_2) > 1/2$, (A5) is satisfied whenever $\mu_1 < \mu_2$ or $F_1 > F_2$.

To determine the robustness of these conclusions and the degree of correspondence between the exact criterion (A5) and the heuristic condition (A3), numerical calculations were performed with randomly chosen parameter values. Let $X \sim U(a, b)$ indicate that X is a random variable with a uniform distribution on (a, b), and let $\mu_{max}(s_f, s_h)$ denote the critical value of μ given by (3b). I first found random parameters for genotype A_2 that produce a stable infection polymorphism by sequentially choosing: $s_{f_2} \sim U(0, 1)$, $s_{h_{02}} \sim U(s_{f_2}, 1)$, and $\mu_2 \sim U(0, \mu_{max}(s_{f_2}, s_{h_{02}}))$. To examine the robustness of the conclusion that selection acts against variants that produce $s_{h_{12}} > 0$ or $s_{h_{21}} > 0$, random equilibria were found, then $U(0, 1)$ values for $s_{h_{12}}$ and $s_{h_{21}}$ were chosen. In 100,000 replicates, (A5) was never satisfied. Similarly, to test the robustness of the prediction that selection decreases μ and increases F, random equilibria were found, then random values chosen that either satisfy or fail the conjectured invasion condition. For instance, to test the conjecture that $F_1 > F_2$ always ensures invasion, irrespective of the values of the other parameters or the magnitude of $F_1 - F_2$, random equilibria were found, then $F_1 \sim U(F_2, 1)$ chosen. No counterexamples were found in 100,000 replicates of each of the four possible tests.

The numerical correspondence between (A5) and (A3) was explored by first finding random equilibria, then choosing parameter values for A_1 according to: s_{f_1}, $s_{h_{01}}$, $\mu_1 \sim U(0, 1)$, $s_{h_{21}} \sim U(0, s_{h_{01}})$, and $s_{h_{12}} \sim U(0, s_{h_{02}})$. For each combination of parameters, condition (A3) was checked; and if it was satisfied, (A5) was checked. Of 100,000 replicates, 14.8% satisfied the heuristic invasion criterion (A3), and 95.9% of these also satisfied the exact condition (A5).