



Host–Parasite Arms Race in Mutation Modifications: Indefinite Escalation Despite a Heavy Load?

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If constantly changing genotypes are favorable in host and parasite coevolution, an indefinite escalation of mutation rates would result despite heavy mutational loads. We theoretically study this possibility by examining the mutation modifier dynamics of host and parasite that engage in genotype-specific epidemiological interaction. In the first model, we study the evolutionarily stable (ESS) mutation rate or switching rate if two alleles in a single locus are subjected to frequency-dependent selection favoring the rarer of the two. Mutation modifier locus is either tightly linked or unlinked to the selected locus. Sufficiently strong frequency-dependent selection may cause cycles in allele frequencies, and a modifier with higher mutation rate enjoys the long-term advantage by randomizing the genotype of their offspring. Through the repeated events of invasion and replacement of mutation modifiers, the mutation rate continues to increase until the allele frequencies are stabilized. If some fraction of mutations are deleterious, there is no longer a pure ESS mutation rate: the evolutionarily stable population then consists of multiple strains concerning mutation modifier, typically one with a very high mutation rate and the other with a very low rate, stably coexisting and fighting off invasions by any other modifiers. These results are almost independent of the linkage between the selected and the modifier loci.

In the second model, we consider the joint evolution of host and parasite mutation modifiers, assuming that a specific pair of host and parasite genotype densities change following the Nicholson–Bailey type model. If there is no cost of deleterious mutations, mutation rates of both species are escalated indefinitely by modifier evolution until they completely suppress the fluctuation of genotype densities. However, a small cost of deleterious mutation is enough to collapse this coevolutionary equilibrium of inflated mutations. Typical coevolutionary outcome is that the parasite mutation rate is accelerated to a high level; whereas the host mutation rate is driven to zero. Extension of our results to host–parasite coevolution of recombination modifier evolution is discussed.

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Introduction

Common genotypes, that may be currently advantageous over others, will often see bad years in the near future, as they are likely to be exploited and attacked by specific predators or parasites. Hence, the fitness of a genotype could be negatively correlated to its frequency in the population. This rare-type advantage would continue to exist if the genotype frequencies fluctuate indefinitely. This idea led Hamilton (1980) and others to hypothesize that sex and recombination would have evolved and main-

tained by parasites: the population with sex and recombination would enjoy an advantage over their asexual counterparts, by producing new rare genotypes that could evade the parasites directed to the currently common genotypes. In other words, randomizing offspring genotypes by recombination would be favored if genotype frequencies fluctuate over time due to antagonistic frequency dependent selection (Jaenike, 1978; Hamilton, 1980; Bremermann, 1980; 1985; Hamilton *et al.*, 1990; Hutson & Law, 1981).

A similar process could apply for the evolution of mutation rate. A sufficiently high mutation, like recombination, would be effective in randomizing

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offspring genotypes and in evading parasites, which we will examine in this paper. This possibility seems to have attracted less attention in the literature, because a high mutation rate should be much more likely to be harmful to an organism than a high recombination rate. Some organisms, however, have genetic devices to localize mutation to a few specific sites or genes: e.g. flip-flop mutations and antigen switching systems in parasitic bacteria and protozoa (Birkbeck & Penn, 1986; Borst & Greaves, 1987). Furthermore, we will show that a very high mutation rate could evolve even if a large proportion of mutation is unconditionally deleterious or lethal, a result previously obtained for the different systems (Sasaki, 1994).

If randomizing its offspring is favorable for a host to evade parasites, it is also favorable for a parasite. Another purpose of this paper is to clarify the consequence of coevolutionary game played between host and parasite through mutation modifications. The coevolution of host and parasite mutation rates have been analysed by Nee (1989) assuming a gene-for-gene association between a host and a parasite genotype. Nee has concluded that mutation rate should increase indefinitely in both host and parasite (see also Ikegami & Kaneko, 1990). The present model extends some of Nee's results to more general cases—we take into account the density dependence via an epidemiological process (as well as frequency dependence) in host-parasite genotype dynamics, and allow more general setting in modifier dynamics (e.g. arbitrary number of modifier alleles, and arbitrary linkage between a modifier and the target selected locus). However, a crucial difference between Nee's results and ours is that we consider the effect of deleterious mutation. It will be shown below that a small amount of deleterious mutation drastically changes the coevolutionary outcome, which is no longer a simple escalation of mutation rates in both species.

The effect of linkage between a modifier and the selected locus is yet another objective of the paper. Consequence of the modifier evolution may critically depend on the extent to which the modifier is linked to the selected locus. ESS mutation rate or ESS recombination rate in a temporally fluctuating environment could be considerably smaller (especially for weak and non-periodic fluctuations), if the modifier locus is unlinked rather than if it is tightly linked (Charlesworth, 1976; Sasaki & Iwasa, 1987; Ishii *et al.*, 1989). We will show, rather surprisingly, that the ESS mutation rate under frequency-dependent selection is almost independent of the linkage between the modifier and the selected locus.

The coevolutionarily stable equilibrium that we examine in this paper is based on the modifier dynamics in host and parasite populations—throughout the paper we examined the evolution of mutation rate by assuming that there is an additional modifier locus other than the selected one, and alleles in the modifier locus adjust the mutation rate of the selected locus differently. Modifier alleles then compete with each other in the population. After the repeated events of invasion and replacement in the modifier locus, the population will reach an equilibrium in which no other modifier can invade. The mutation rate thus evolved is called the ESS mutation rate (Lieberman & Feldman, 1986; Ishii *et al.*, 1989). If mutation modifier dynamics of both host and parasite lead to a jointly stable equilibrium, i.e. if a set of host and parasite mutation modifiers respectively does not allow the invasions of any other modifiers in each population, we call this the coevolutionarily stable mutation rate.

This is a natural extension of game-theoretical ESS concept to the one with an explicit population genetical background—the latter is called the evolutionary genetic stability (EGS) by Eshel & Feldman (1982). In general, a given coevolutionary dynamics does not necessarily have the same set of pure strategies that the joint ESS has, because the evolutionarily stable population could be polymorphic (a coalition of strategies that refuses the invasions by any others—Brown & Vincent, 1987; Ludwig & Levin, 1992; Ellner & Hairston, 1994; Sasaki & Ellner, 1995). Indeed, we will show that in a simple model of frequency-dependent selection with non-zero mutational load, the population evolves to the state in which multiple modifiers stably coexist. We also discuss the possibility that an indefinite escalation of mutation rate might drive the population to extinction by causing too many lethal mutations.

To summarize, we will examine in the present paper how ESS mutation rate depends on the intensity of frequency-dependent selection, the fraction of deleterious mutation, and the linkage between modifier and the selected locus. We then examine the coevolution of host and parasite mutation rates if there is gene-for-gene interaction between their genotypes, and show how the coevolutionary process depends on the epidemiological and genetic parameters. The model rather surprisingly reveals that even if there is no such asymmetry as unequal generation times or unequal genome sizes between host and parasite, the coevolutionary trajectory tends to reach a quite asymmetrical equilibrium with no mutation in host and very high mutation in parasite.

Frequency-dependent Selection Model

We consider a haploid organism and focus on two alleles, A and a , in a single locus subjected to frequency-dependent selection favoring the rarer of the two alleles. Specifically we assume that the fitness of an allele decreases exponentially with its frequency x in the population:

$$w(x) = \exp(-\beta x), \quad (1)$$

where β is a positive constant indicating the strength of frequency-dependent selection. The underlining mechanism of this frequency dependence could be the specific antagonistic interaction between host and parasite genotypes (e.g. a gene-for-gene system). Clearly this is a simplifying assumption, and a straightforward epidemiological model of host and parasite genotypes will be examined later to confirm the generality of the conclusions reached thereafter. The population is infinitely large and panmictic. Generations are non-overlapping. Symmetric mutation between alleles A and a follows selection in each generation. The mutation rate is determined by a modifier in the second locus. Specifically, allele M_i in the modifier locus adjusts the mutation rate at the selected locus to μ_i per generation. Letting p_{is} be the frequency of haplotype $M_i s$ ($s \in \{A, a\}$), the haplotype frequencies in the next generation are:

$$p'_{is} = (1 - \mu_i) \frac{w(p_s)p_{is}}{\bar{w}} + \mu_i \frac{w(p_{\bar{s}})p_{i\bar{s}}}{\bar{w}},$$

with $\bar{w} = w(p_s)p_s + w(p_{\bar{s}})p_{\bar{s}}$ (2)

provided that the modifier and the selected loci are tightly linked. Here $\bar{s} = a$ if $s = A$, and $\bar{s} = A$ if $s = a$; $p_s = \sum_i p_{is}$ is the frequencies of alleles s ($s \in \{A, a\}$) in the population ($p_s + p_{\bar{s}} = 1$ by definition).

INVASIBILITY ANALYSIS

If the population consists of a single mutation modifier with mutation rate μ , then the frequency, x , of the A allele in the selected locus changes as

$$x' = (1 - \mu) \frac{w(x)x}{\bar{w}_0} + \mu \frac{w(1-x)(1-x)}{\bar{w}_0},$$

with $\bar{w}_0 = w(x)x + w(1-x)(1-x)$. (3)

The dynamical behavior of the one-dimensional map (3) is very simple: if the mutation rate is larger than a threshold, which will be defined below, then the steady state $x = 1/2$ is globally stable. Decreasing μ past the threshold μ_c leads to a flip (period-doubling) bifurcation, resulting in a stable two-point cycle around $x = 1/2$. No further bifurcation occurs as $\mu \rightarrow 0$ (Fig. 1). The threshold mutation rate exists for

$\beta > 4$ (otherwise, the steady state $x = 1/2$ is globally stable for all μ), and

$$\mu_c = \frac{\beta - 4}{2(\beta - 2)}. \quad (4)$$

As the intensity β of frequency-dependent selection increases, the threshold mutation μ_c needed to stabilize the system increases, which approaches to the maximum value $1/2$ as $\beta \rightarrow \infty$.

Now we examine whether or not a modifier M_1 with the mutation rate ν can invade the wild-type M_0 population with mutation rate μ . We here assume that the modifier and the selected locus is completely linked, and discuss the effect of loose linkage later. To simplify the analysis, we denote the frequency of M_i -modifier by $\phi_i = \sum_s p_{is}$ ($i = 0, 1$), the relative frequencies of allele A in M_0 -populations by $x = p_{0A}/\phi_0$, and that in M_1 -population by $y = p_{1A}/\phi_1$. The genotype frequencies are then rewritten as $p_{0A} = \phi_0 x$, $p_{0a} = \phi_0(1-x)$, $p_{1A} = \phi_1 y$, and $p_{1a} = \phi_1(1-y)$. We can derive the recursion equations for x , y and $\phi = \phi_1$ from (2), assuming that the M_1 -modifier is rare. First, the recursion for the frequency of allele A in M_0 population is given by (3). Second, the frequency of the A allele in M_1 population changes as

$$y' = (1 - \nu) \frac{w(x)y}{\bar{w}_1} + \nu \frac{w(1-x)(1-y)}{\bar{w}_1},$$

with $\bar{w}_1 = w(x)y + w(1-x)(1-y)$. (5)

As shown above, x_i converges to $1/2$ if $\mu > \mu_c$ and it fluctuates with period 2 if $\mu < \mu_c$. Recursion eqn (5)

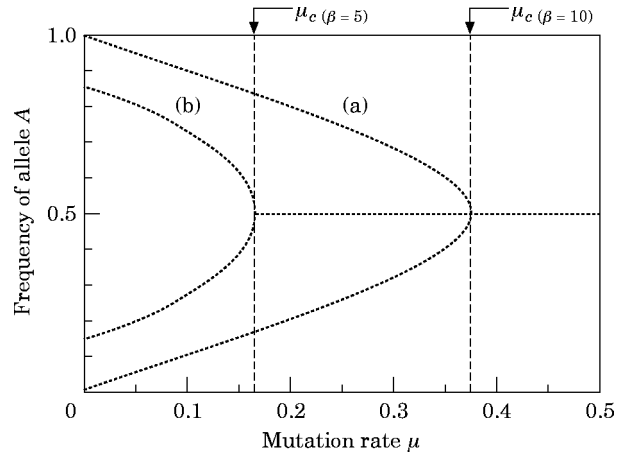


FIG. 1. Phase portrait for the one-dimensional map (3). The bifurcation point μ_c (dashed line) depends on the strength of selection β . For $\mu < \mu_c$, the dynamics converge to a stable cycle with period 2, which is symmetric around $1/2$. For $\mu > \mu_c$, the dynamics are stabilized at the equilibrium $x = 1/2$. (a) $\beta = 10.0$; (b) $\beta = 5.0$.

for y_t after the initial transient is therefore regarded as a one-dimensional map with the constant $x_t (= 1/2)$ if $\mu > \mu_c$, and that with varying coefficient x_t taking two values alternatively if $\mu < \mu_c$. Standard analysis of (5) reveals that the dynamical behavior of y_t inherits that of x_t : y_t converges to $1/2$ if $\mu > \mu_c$, and it converges to a two-point cycle if $\mu < \mu_c$, with the amplitude depending on the difference between v and μ .

Final recursion equation to complete the modifier dynamics is that for the frequency of M_1 modifier $\phi = \phi_1$, which is simply given by

$$\phi' = \frac{\bar{w}_1}{\bar{w}_0} \phi. \quad (6)$$

Therefore, the fate of a mutant modifier is determined by the marginal log growth rate

$$\begin{aligned} \lambda(v|\mu) &= E_t \log \left\{ \frac{\bar{w}_1}{\bar{w}_0} \right\} \\ &= E_t \log \left\{ \frac{w(x_t)y_t + w(1-x_t)(1-y_t)}{w(x_t)x_t + w(1-x_t)(1-x_t)} \right\} \\ &= E_t \log \left[1 + \frac{\{w(x_t) - w(1-x_t)\}(y_t - x_t)}{\bar{w}_0} \right]. \end{aligned} \quad (7)$$

The mutant modifier invades the population if $\lambda(v|\mu)$ is positive, and fails to invade if $\lambda(v|\mu)$ is negative. Here the expectation represents the long-term average over generations t (remind that allele frequencies $x = x_t$ and $y = y_t$ fluctuate if $\mu < \mu_c$). From eqn (7), we see that the invasibility of mutant depends on the extent to which the allele frequencies in the selected loci are regulated by mutation.

The course of modifier evolution could be predicted from the following argument: note first that x_t alternates around $1/2$ if $\mu < \mu_c$. Quick inspection of the last term of (7) then reveals that for generations with $x < 1/2$ ($w(x) > w(1-x)$ by minority advantage), the mutant modifier increases if $y > x$. Conversely, for generations with $x > 1/2$, mutant increases if $y < x$. Therefore, mutant modifier can invade if $|y_t - 1/2| < |x_t - 1/2|$, i.e. if the allele frequency in mutant population is more tightly regulated than that of wild type. This suggests an advantage of having higher mutation rate than wild type, and the indefinite increase of mutation rate through modifier evolution.

Indeed we can prove the following result in Appendix A:

- If the wild type mutation rate is below the threshold, any modifier of larger mutation rate than the wild type can always invade the population.

As the simplest example, consider the fate of the modifier with the mutation rate $v = 1/2$. This modifier can always invade the population with $\mu < \mu_c$, because it keeps the allele frequency in the mutant population at $1/2$ ($y_t = 1/2$ for all t). We also note that any mutation rate larger than the threshold (4) is a (weak) ESS: Since the frequency of allele A in the wild type population converges to a constant, we have $\lambda(v|\mu) = 0$ for all v .

NUMERICAL SIMULATION

To confirm the above conclusions based on the invasibility analysis of a mutant modifier, we analysed the modifier dynamics (2) numerically, assuming that there are 100 alleles in the modifier locus with equally separated effects from $\mu = 0$ to $\mu = 0.5$. As noted above, we assumed that the modifier and the selected locus is completely linked. The initial distribution of modifiers was concentrated at $\mu = 0$ (we adopted an exponential distribution with a sharp mode at $\mu = 0$). Figure 2 demonstrates the typical results of modifier evolution, indicating that the modifier distribution continues to evolve to the right (i.e. for the direction of higher mutation rate), and then stop drifting when the peak exceeds the threshold mutation rate. Figure 3 illustrates that the population mean mutation rate increases monotonically with time until

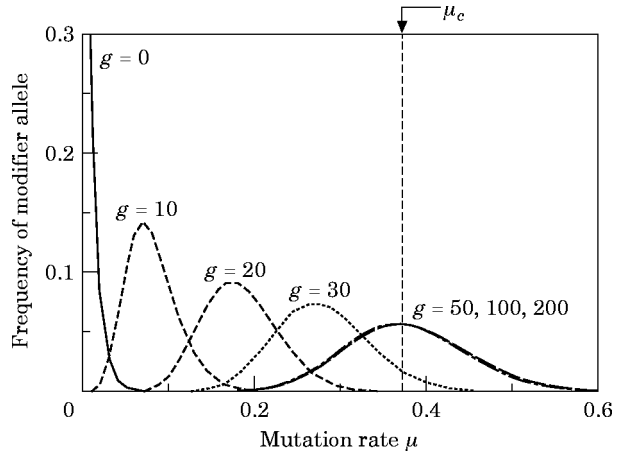


FIG. 2. Distributions of mutation rate in the population at generations $g = 0, 10, 20, 30, 50, 100$ and 200 . The population at $g = 0$ almost consists of a modifier with $\mu = 0$ (Initial distribution was set to be an exponential at the peak $\mu = 0$.) Unimodal distribution continues to move to the right, but around $g = 50$ the peak of the distribution reaches μ_c (dashed line) and thereafter the distribution almost stopped shifting. $\beta = 10.0$.

it exceeds the threshold (dashed line). We examined the modifier dynamics for various intensities of selection (i.e. for various values of β), but the qualitative results were the same—the only differences are that the threshold mutation rate changes by β according to (4), and for $\beta < 4$ no modifier evolution occurs because allele frequency in the selected loci is stabilized by any mutation rate.

We must note here that the final shape of modifier frequency distribution is “neutrally stable”, in the sense that what shape is finally reached as a steady state depends on the initial distribution, and even after the convergence to the steady state, it would be vulnerable to changes by the random disturbance. This is because no causal change occurs if the allele frequency is stabilized by a sufficiently high mean mutation rate. Our conclusion is not the final shape but the fact that as long as the mean mutation rate is lower than the threshold, so that the allele frequency in the selected loci oscillates, the modifier distribution moves toward higher mutation rate.

An ESS mutation rate (note that any mutation rate greater than the threshold μ_c is ESS) reached in modifier evolution is very different from the optimal mutation rate that maximizes the geometric mean fitness of the population. The asymptotic expansion of the optimal mutation rate for large β is derived in Appendix B, which indicates that the optimal mutation rate decreases towards zero with increasing β , while the ESS mutation rate approaches to 0.5. Thus, for a sufficiently strong selection, the ESS mutation rate is much larger than the optimal, indicating that the population mean fitness could become very low at the ESS. This suggests that the arms race in mutation modification would drive the population to extinction. Figure 4 shows an example

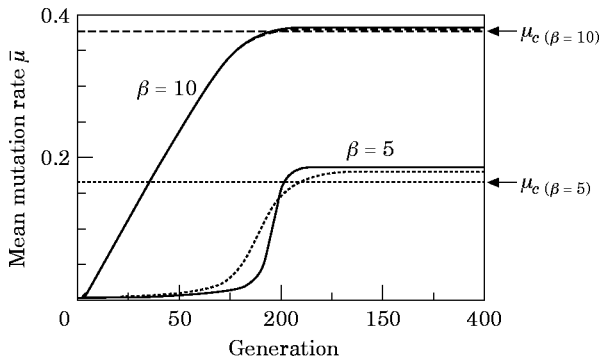


FIG. 3. The mean mutation rate in population as a function of time observed in the modifier evolution. The initial mean mutation rate was set to be very low. The mean mutation rate increases until it exceeds the threshold μ_c (dashed horizontal lines). Solid curves, tightly linked modifiers ($c = 0$); dashed curves, unlinked modifiers ($c = 0.5$). Results for both $\beta = 5$ and $\beta = 10$ are shown in each cases.

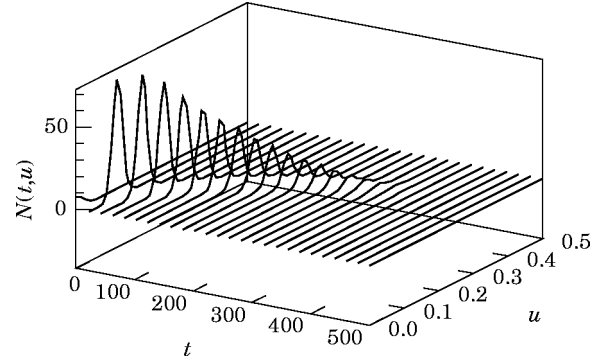


FIG. 4. Population extinction by the evolution of mutation rate. The allele frequencies are assumed to change according to (2) in the text, with $\beta = 10$. We additionally assume that the total density N_i changes as $N_{i+1} = a\bar{w}N_i/(1 + bN_i)$, with $a = 100$, $b = 0.01$, and \bar{w} defined in (2). Evolution of the absolute density distribution of mutation rates, $N(t, \mu)$, is plotted. Initially low mutation rate continued to be escalated to a high level (as high as $\bar{\mu} = 0.35$), thereby reducing the population mean fitness. The population was finally driven to extinction. The optimal mutation rate that maximizes the geometric mean fitness was about $\mu = 0.1$.

of numerical simulations in which this type of population extinction occurred.

To summarize, the mutation rate continues to increase through the modifier evolution, because a mutant randomizing its offspring further than the wild type can always invade the population. This unidirectional evolution stops only when the mean mutation rate exceeds μ_c and the population dynamics are completely stabilized.

EFFECT OF LINKAGE TO MODIFIER LOCUS

In the previous studies of modifier evolution in temporally fluctuating environments, it has been shown that the linkage between the selected and the modifier loci could greatly affect the ESS mutation and recombination rates (Charlesworth, 1976; Sasaki & Iwasa, 1987; Ishii *et al.*, 1989). We here examine the effect of linkage, assuming that the events occur in the order of selection, mutation, and recombination in a generation. Adding recombination to the modifier dynamics (3), (5–6) only changes the recursion for the allele frequency y in the mutant modifier population as

$$y_{i+1} = (1 - v)y_i^* + v(1 - y_i^*) + c \frac{(1 - 2\mu)}{\bar{w}_1} \{1 - 2x_i^*\} \quad (5')$$

while the other eqns, (3) and (6), are unchanged, as far as the mutant modifier is rare. Here, symbols with asterisks* denote the quantities after selection, and c is the recombination rate between the modifier and the selected loci.

Numerical analysis revealed that there is no significant difference in the ESS mutation rate between completely linked and completely unlinked models (Fig. 3). Only when the strength of the selection is very close to the threshold (i.e. for β slightly larger than four), the rate of evolution could vary with linkage. However, both the time to reach the steady state and the mean mutation rate in a steady-state population are similar for linked and unlinked cases. These results are very different from the results of the ESS mutation and recombination rates for externally fluctuating environments (Charlesworth, 1976; Sasaki & Iwasa, 1987; Ishii *et al.*, 1989), in which ESS mutation or recombination rate is very small if the modifier locus is unlinked to the selected locus.

EFFECT OF DELETERIOUS MUTATION

So far we have analysed the evolution of mutation rate provided that a mutation only changes the allelic state at a locus subject to frequency-dependent selection. However, if the mutation modifier affects the mutation rate of any sites in the genome, a higher mutation rate causes an increased number of deleterious changes in conservative and functionally important sites in the genome. Only those mutations occurred at a limited number of sites in the genome would contribute to the adaptive changes to escape from parasite.

Here we consider the effect of deleterious mutation by assuming that all but a small fraction of mutations are lethal, so that the strain with a higher mutation rate should suffer significant cost of deleterious mutation. Specifically, we assume that a fixed fraction Q ($0 < Q < 1$) of mutations contribute to change the allelic state in the locus under frequency dependent selection, and the rest of mutations are lethal. We first consider the case in which the selected locus is tightly linked to the modifier locus. The frequency dynamics of monomorphic modifier population is then

$$x' = \frac{1}{\sigma_\mu} \left\{ (1 - \mu) \frac{w(x)x}{\bar{w}_0} + \mu Q \frac{w(1-x)(1-x)}{\bar{w}_0} \right\}, \quad (8)$$

where μ is the mutation rate of the wild type, $\sigma_\mu = 1 - \mu + \mu Q$ is the survivorship through mutation (because the fraction $(1 - Q)\mu$ of progeny are the lethal mutants), and $\bar{w}_0 = w(x)x + w(1-x)(1-x)$ is the mean fitness (without the load by deleterious mutations). The dynamical behavior of (8) is qualitatively the same as that of (3): there is a threshold mutation rate μ_c such that the frequency is stabilized at $x = 1/2$ if $\mu > \mu_c$, and it exhibits a

two-point cycle if $\mu < \mu_c$. The threshold mutation rate (4) becomes

$$\mu_c = \frac{\beta - 4}{(1 + Q)\beta - 4} \quad (9)$$

so that for a very large cost of deleterious mutation (small Q) and for a very strong frequency-dependent selection (large β), the threshold μ_c approaches to one instead of a half. The frequency of allele A in the newly introduced mutant modifier changes as

$$y' = \frac{1}{\sigma_v} \left\{ (1 - v) \frac{w(x)y}{\bar{w}_1} + vQ \frac{w(1-x)(1-y)}{\bar{w}_1} \right\}, \quad (10)$$

where v is the mutation rate produced by the mutant modifier, $\sigma_v = 1 - v + vQ$, and $\bar{w}_1 = w(x)y + w(1-x)(1-y)$. The frequency of the mutant modifier changes as

$$\phi' = \frac{\sigma_v \bar{w}_1}{\sigma_\mu \bar{w}_0} \phi. \quad (11)$$

The invasibility of mutant modifier is determined by the sign of marginal growth rate

$$\lambda(v|\mu) = E \log \left\{ \frac{1 - v + Qv}{1 - \mu + Q\mu} \right\} + E \log \left\{ \frac{w(x)y + w(1-x)(1-y)}{w(x)x + w(1-x)(1-x)} \right\}. \quad (12)$$

Thus, the ESS mutation rate is affected by an additional effect of deleterious mutation, as shown in the first term of the r.h.s. of eqn (12). The results of invasibility analysis based on (8–12) are summarized as follows (see Fig. 5 that illustrates $\lambda(v|\mu)$ as a function of v):

- (i) If the wild type's mutation rate μ is sufficiently smaller than the threshold, $\lambda(v|\mu)$ is monotonically increasing function of v with $\lambda(\mu|\mu) = 0$, indicating that if the mutant's mutation rate is higher than the wild type's, the mutant modifier can invade.

Hence the population mean mutation rate increases through modifier evolution, until it approaches to the threshold. However, if the mean mutation rate comes too close to the threshold, modifiers with a very small mutation rate become able to invade:

- (ii) For the wild type's mutation rate sufficiently close to the threshold, $\lambda(v|\mu)$ becomes positive for a sufficiently small v (and the highest for $v = 0$), indicating that modifiers with very small mutation rate can invade the population.

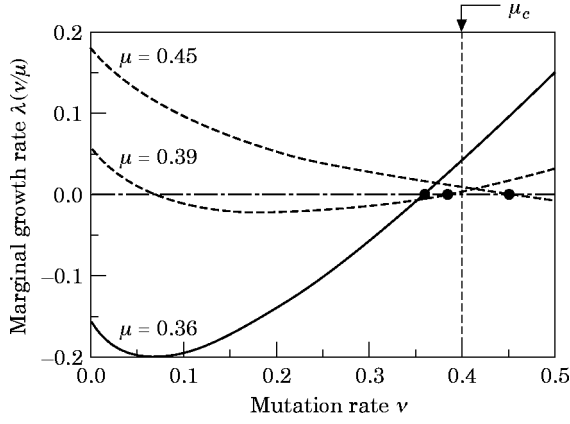


FIG. 5. The marginal growth rate $\lambda(v|\mu)$ as the function of mutant's mutation rate v , for several values of wild type mutation rates $\mu = 0.36, 0.39$ and 0.45 . To evaluate λ , we need to know the allele frequency data $\{x_i\}$ and $\{y_i\}$ in wild type and mutant modifier populations. We first obtained stable 2-periodic points x_1 and x_2 of the map (8) to get $\{x_i\} = \{x_1, x_2, x_1, x_2, \dots\}$. We then calculated stable 2-periodic points y_1, y_2 of the map (10) using the data $\{x_i\}$ obtained above to have $\{y_i\} = \{y_1, y_2, y_1, y_2, \dots\}$. The marginal growth rate λ for each values of wild type's and mutant's mutation rates μ and v respectively, were thus calculated from (12) using these time series data $\{x_i\}$ and $\{y_i\}$. Threshold mutation rate is $\mu_c = 0.4$ (dashed vertical line).

This implies that if the mutation rate is so enhanced that the amplitude of the fluctuation of allele frequencies becomes small, the effect of direct cost of producing deleterious mutants dominates the selective advantage for a still higher mutation rate. Hence the mutation modifier with $\mu = 0$ can invade because it is free from the cost of lethal mutations. On the other hand, if the wild type mutation rate is $\mu = 0$, a modifier with a positive mutation rate can invade. This therefore suggests that there is no pure ESS.

Indeed, numerical analyses of the modifier dynamics with a large number of modifier alleles of different effects demonstrated that the evolutionarily stable

population is dimorphic with respect to mutation rate—in the ES population, a modifier with possible minimum mutation rate and a modifier with a very high mutation rate coexist, and this dimorphic population refuses further invasion by any other modifiers (Fig. 6). Numerical analyses also revealed that if we further increase the fraction of deleterious mutations (i.e. decrease Q), the population would evolve to a trimorphism, consisting of three modifiers with zero, medium, and extremely high mutation rates.

Adding recombination between the modifier and the selected locus again failed to show any significant difference.

MANY ALLELES IN THE SELECTED LOCUS

We here examine the extension of our results to the cases where more than three alleles are segregating in the population. Assume that n alleles $A_1 A_2 \dots A_n$ ($n > 2$) are segregating in the selected locus, and that the fitnesses of different genotypes are given by (1). An allele A_k is assumed to change by mutation to one of the other alleles A_l ($k \neq l$) with the same probability. As before, we consider a tightly linked modifier locus, such that an allele M_i in the modifier locus adjust the total mutation rate at selected locus to μ_i per generation. Hence the mutation rate from A_k to A_l is given by $\mu_i/(n-1)$. Letting p_{ik} be the frequency of haplotype $M_i A_k$, the frequencies in the next generation are

$$p'_{ik} = \frac{(1 - \mu_i)w(p_k)p_{ik} + \mu_i \sum_{l \neq k} w(p_l)p_{il}/(n-1)}{\bar{w}}, \quad (13)$$

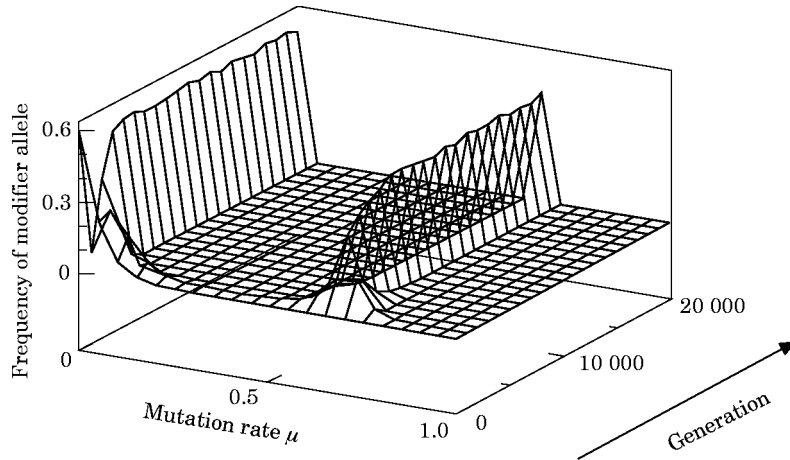


FIG. 6. The frequency distribution of mutation rate converging to a dimorphic distribution with peaks at $\mu = 0$ and at $\mu = 0.65$. Other parameters are: $\beta = 10$, $Q = 0.9$.

where $p_k = \sum_i p_{ik}$ is the frequency of allele A_k in the population, and $\bar{w} = \sum_k \sum_i w(p_k) p_{ik}$ is the population mean fitness.

Analysis similar to the one used for two allele case establishes the following results:

- (i) There is the threshold mutation rate for the local stability of isoplethy equilibrium $\hat{p}_1 = \dots = \hat{p}_n = 1/n$:

$$\mu_c = \frac{(n-1)(\beta-2n)}{n(\beta-n)}. \quad (14)$$

If the wild-type mutation rate is larger the threshold (14), then the equilibrium is locally stable, and hence all the alleles are stably maintained with the same frequency $1/n$. If the mutation rate is smaller than the threshold, then the population exhibits two-point cycles of the frequency of each allele.

- (ii) Numerical analysis of the modifier dynamics (13) reveals qualitatively the same results as two allele model: The mean mutation rate increases towards μ_c through modifier evolution, and this unidirectional evolution stops when the mean mutation rate exceeds μ_c (Fig. 7).
- (iii) The threshold mutation rate (14) is zero if the number of alleles n in the selected locus is larger than $\beta/2$. In other words, if the population is highly polymorphic at the selected locus, the evolution for a still higher mutation rate is unlikely to occur.

Later we will discuss the potential effect of random genetic drift on the last result (see Discussion).

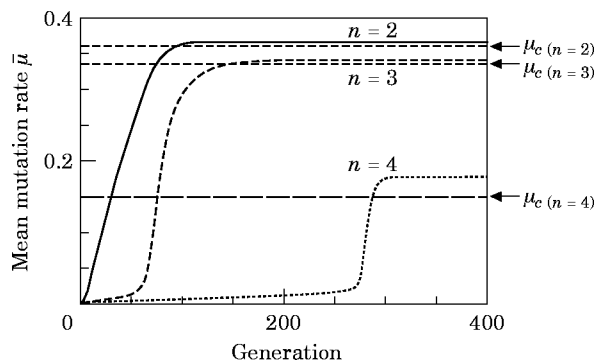


FIG. 7. The population mean mutation rate in the simulation of modifier dynamics with the number of alleles in the selected locus: $n = 2, 3$ and 4 . $\beta = 9.0$. We assumed that there are 200 modifier alleles with evenly separated effects from $\mu = 0$ to $\mu = 0.5$ (the upper limit of μ was chosen so that it must be larger than the threshold for any examined values of n and β). Initial distribution of modifiers was concentrated sufficiently strongly at $\mu = 0$. In all the cases, the mutation rate increases until it exceeds the threshold (denoted by dashed lines). As the allele number increases, the evolutionarily stable mutation rate decreases.

Coevolution of Host and Parasite Mutation Rates

We analysed the evolutionary effect of parasites as the frequency-dependent selection on the host, which is expected under host-parasite gene-for-gene interaction. If a higher mutation rate is favorable for the host to evade parasite, the same must be true for the parasite because parasite needs to match the host's changing genotype. In this section, we explicitly consider the epidemiological dynamics of host and parasite genotypes, and examine the mutation modifier evolution in both species.

Closely related to our model was studied by Nee (1989), who showed that assuming an antagonistic interaction between host and parasite genotypes, higher mutation rates are always favored in both species, until the enhanced mutation rates are enough to stabilize the genotype dynamics. We here study the effect of deleterious mutation, which was neglected in Nee (1989), by assuming that only a fraction of mutations contribute to changes in the allelic state of immunologically important sites, and the other fractions are deleterious.

Without this deleterious effect of mutations, we obtained essentially the same result as Nee's (1989): there is a coevolutionarily stable curve of equilibria toward which mutation rates of host and parasite are enhanced through modifier evolution. On this curve, both parasite and host have intermediately high mutation rates. However, it will be shown below that this curve of equilibria is "neutrally stable" in coevolution. Adding a small amount of deleterious mutation is enough to collapse the high-mutation-high-mutation equilibria, leading to the evolution of very high mutation rate in one species (typically, parasite) and of possible minimum mutation rate in the other (host). This asymmetrical equilibrium is purely an outcome of coevolutionary process—if the mutation rate of either species were fixed at a low level, the mutation rate of the other species would evolve to a very high level. In the following, we examine these results in greater detail.

NICHOLSON–BAILEY MODEL

We adopt the Nicholson–Bailey model for the epidemiological dynamics of specific host and parasite genotypes. We assume that both host and parasite are haploid with non-overlapping generations. In each generation, parasitization and growth is followed by the mutation in both host and parasite.

Let H_i and P_i be the host and parasite densities with allele i ($i = A, a$). We assume the parasite genotype i

is specialized to attack the host genotype i , so that the densities before mutation are

$$H_i^* = H_i \exp\{r(1 - H/K) - \beta P_i\}, \quad (15a)$$

$$P_i^* = H_i[1 - \exp(-\beta P_i)], \quad (15b)$$

where $H = H_A + H_a$ is the total host density; $\exp(r)$, the intrinsic finite rate of growth of the host; K , the carrying capacity of the host; β , the search efficiency of the parasite. Fertile hosts and parasites then undergo mutation with the rates μ_H and μ_P , respectively, and the fraction of successful mutations, Q_H and Q_P , respectively ($0 < Q_H, Q_P \leq 1$). The genotype densities in the next generation are:

$$H'_i = (1 - \mu_H)H_i^* + \mu_H Q_H H_j^*, \quad (16a)$$

$$P'_i = (1 - \mu_P)P_i^* + \mu_P Q_P P_j^*, \quad (16b)$$

where $j = a$ if $i = A$ and $j = A$ if $i = a$. Here, the first term on the r.h.s. represents the contribution from the individuals that do not undergo mutation, and the second term represents contributions from the successful mutants. This implies that the fraction $(1 - Q_H)\mu_H$ of host progenies and the fraction $(1 - Q_P)\mu_P$ of parasite progenies are lethal mutants, which do not contribute to the next generation at all.

Before proceeding to the mutation modification dynamics, we browse how the dynamics depend on the residual mutation rates, μ_H and μ_P , of host and parasite. Local stability analysis of the internal equilibrium (Appendix C) reveals that there is a curve on $\mu_H - \mu_P$ plane above which the population is stabilized at the internal equilibrium. As the parameter decreases below the curve, the *Hopf* bifurcation occurs and both total densities and allele frequencies of host and parasite converge to limit cycles.

MODIFIER DYNAMICS

We first analyse whether or not a newly introduced host modifier with the mutation rate $v_H (\neq \mu_H)$ can invade the population with the wild-type host mutation rate μ_H and the parasite mutation rate μ_P . The population densities H_i and P_i of wild types change following (15) and (16). Let h_i be the density of host with allele i ($i = A, a$) in the selected locus, and having mutant modifier v_H in the modifier locus. The genotype densities of mutant host when rare change by growth and parasitism as

$$h_i^* = h_i \exp\{r(1 - H/K) - \beta P_i\}, \quad (17a)$$

where $H = H_A + H_a$ is the wild type host density. Assuming complete linkage between the selected

and modifier locus, these densities change by mutation as

$$h'_i = (1 - v_H)h_i^* + v_H Q_H h_i^*, \quad (17b)$$

where we adopted the same convention as in (16) (e.g. $j = a$ if $i = A$). Combining (17a) and (17b) together, and denoting explicitly the time dependence, the recursion formula for mutant host densities are given by

$$h_i(t+1) = e^{r(1 - H(t)/K)} \{ (1 - v_H) e^{-\beta P_i(t)} h_i(t) + v_H Q_H e^{-\beta P_i(t)} h_i(t) \}. \quad (18a)$$

The invasibility of mutant modifier is then determined by the mean log growth rate of the total mutant modifier density $h = h_A + h_a$:

$$\lambda_H(v_H | \mu_H) = E_t \log \{ e^{r(1 - H(t)/K)} (1 - v_H + v_H Q_H) \times \sum_s x_s(t) e^{-\beta P_s(t)} \}, \quad (18b)$$

where $x_i = h_i/h$ is the relative abundance of genotype i host in the mutant modifier population. The mutant modifier can invade the population if eqn (18) is positive, and fails to invade if it is negative.

Similarly, if the parasite mutant modifier with $v_P \neq \mu_P$ is invading the population with host mutation rate μ_H and the parasite residual mutation rate μ_P , the mutant densities with the allele i in the selected locus changes when rare as follows: the mutant genotype i of parasite before mutation step in a generation is given by

$$p_i^* = H_i (1 - e^{-\beta P_i}) (p_i / P_i). \quad (19a)$$

(There are $H_i [1 - \exp(-\beta(P_i + p_i))]$ of hosts that are parasitized by parasite genotype i , and the fraction $p_i / (p_i + P_i)$ of which were parasitized by parasites with the mutant modifier. Neglecting higher order terms with respect to p_i , we have (19a).) These then change by mutation to have mutant genotype densities in the next generation:

$$p'_i = (1 - v_P)p_i^* + v_P Q_P p_i^*. \quad (19b)$$

The sign of marginal log growth rate of total mutant modifier $p = p_A + p_a$:

$$\lambda_P(v_P | \mu_P) = E_t \log \{ (1 - v_P + v_P Q_P) \times \sum_i (H_i(t) / p_{i(t)}) (1 - e^{-\beta P_i(t)}) y_i(t) \}, \quad (20)$$

where $y_i = p_i/p$, then gives the invasibility criterion.

COEVOLUTIONARILY STABLE MUTATION RATES

The course along which host and parasite mutation rates coevolve could be predicted by dividing the $\mu_H - \mu_P$ plane according to the signs of the selection gradient for modifiers: $\rho_H = (\partial \lambda_H / \partial v_H) |_{v_H = \mu_H}$ and $\rho_P = (\partial \lambda_P / \partial v_P) |_{v_P = \mu_P}$. Numerically, these can be

calculated from the marginal log growth rate (18) and (20), for mutant with mutation rates, v_H and v_P , slightly different from the wild type's, μ_H and μ_P . For example, if ρ_H is positive at the point (μ_H, μ_P) , then the host mutation rate would increase by the invasions of modifiers with higher mutation rates. The same analysis could apply for ρ_P , and combining these two, we can obtain "isoclines" for the coevolutionary trajectory of host and parasite mutation modifier dynamics.

Figure 8 illustrates the coevolutionary trajectories of host and parasite mean mutation rates observed in numerical simulations, together with the curves of "null clines" $\rho_H = 0$, and $\rho_P = 0$ defined above. As before, we simulated the modifier dynamics assuming that there are 100 alleles with equally separated effects from $\mu_H, \mu_P = 0$ to $\mu_H, \mu_P = 1$ in the modifier locus of host and of parasite. The selected locus and the modifier locus may be linked or unlinked. The directions of coevolution predicted by the signs of gradients ρ_H and ρ_P are indicated by arrows. Figure 8 shows that the predictions by the sign of gradients approximate the coevolutionary trajectories observed in computer simulations very well. We have simulated modifier dynamics for 576 combinations of different values of parameters, r (the host intrinsic growth rate), β (parasite searching efficiency), c_H and c_P (the recombination rates between the selected and the modifier locus in host and in parasite), and Q_H and Q_P (the fraction of successful mutations of host and of parasite). The results of these numerical simulations and the selection gradient analysis are summarized as follows:

- (i) If there is no cost of deleterious mutation ($Q_H = Q_P = 1$), the mean mutation rates of both host and parasite were escalated toward one of the points on a curve of equilibria, at which genotype densities stop oscillation (the set of *Hopf* bifurcation points). This is because both ρ_H and ρ_P are positive below this curve and hence modifiers having mutation rate higher than the population means are always favored; and above the curve $\rho_H = \rho_P = 0$. The end points of coevolution thus depend on the initial conditions [Fig. 8(a)].
- (ii) If we introduce a slight cost of deleterious mutations, on the other hand, the neutrally stable curve of high-mutation-high-mutation equilibria collapses into a point, i.e. there is the coevolutionarily stable set of host and parasite mutation rates.

Figure 8(b) illustrates the coevolutionary trajectories for the mean mutation rates for five different initial

states, for the case where a small fraction of mutation is lethal in both host and parasite ($Q_H = Q_P = 0.9$). For example, if we start from the population where mean mutation rate is small for both host and parasite, the mutation rates of both species increase towards the curve $\rho_H = 0$, and then enter into the narrow region between this curve and the curve $\rho_P = 0$. The trajectory then turns to left and move in the region. Finally, it reaches the coevolutionarily stable equilibrium point where $\mu_H^* = 0$ and $\mu_P^* > 0$. Note that we assumed the equal fraction of deleterious mutation for host and parasite ($Q_H = Q_P$). Nevertheless the system evolves to an asymmetrical equilibrium of no (possible minimum) mutation in host and a very high mutation rate in parasite. According to the extensive computer simulations (Tables 1–3), this is a general rule:

- (iii) If other conditions [(a) and (b) below] are the same between parasite and host, then the parasite mutation rate tends to evolve to a high level but the host mutation rate evolves to zero [Fig. 8(b) and (c)].

In other words, it is the host that tends to retreat from the arms race in mutation modifications, other conditions being the same. The result could be very different if only one species evolves. Suppose that the parameters are the same as above and that now parasite mutation rate is not allowed to evolve (i.e. fixed to a low level). Then the host mutation rate increases to a very high level (Fig. 9). This suggests that the reason why host mutation rate evolves to possible minimum is not simply the high mutational load itself, but is because increasing mutation rate does not pay to evade highly mutable parasites.

However, there are several important conditions under which the above rule (iii) no longer applies:

- (a) *Mutational risk*. If the cost of deleterious mutation is considerably higher (i.e. if Q is much smaller) in one species than in the other, then the species with smaller cost tends to evolve to a high mutation rate but the other evolves to zero mutation [Fig. 8(d) and Table 2].
- (b) *Linkage*. If the modifier locus in one species is more loosely linked to the selected locus than in the other species, the one with looser linkage tends to evolve to zero mutation (Table 3).
- (c) *Extreme fluctuation*. If epidemiological parameters are such that host and parasite density fluctuate with extremely large amplitudes, then the mutation rates of both host and parasite could evolve to nonzero level [Fig. 8(e); Table 1, bottom row].

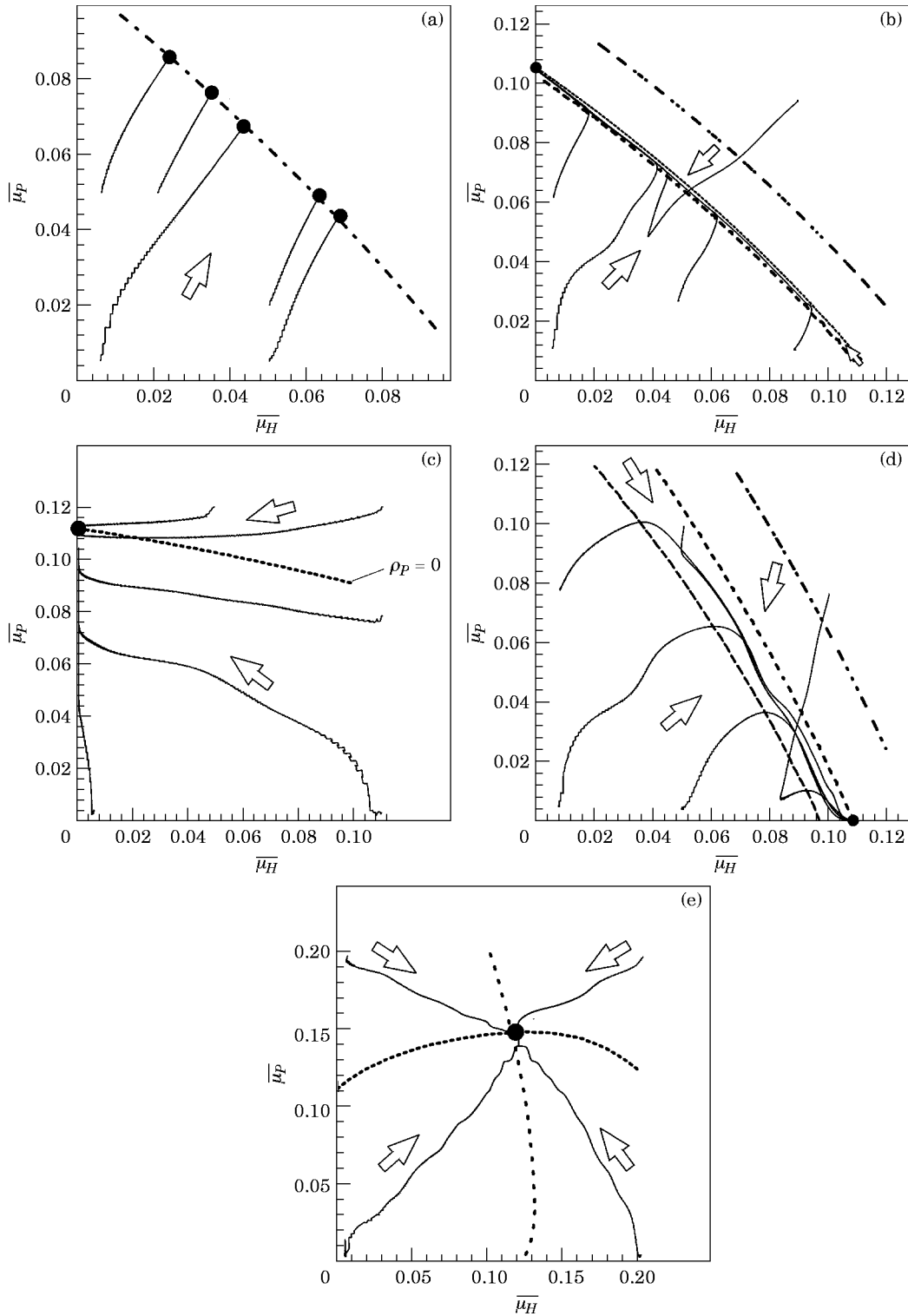


FIG. 8. The coevolutionary trajectories of the population mean mutation rates of host (horizontal axis) and parasite (vertical axis). Three thick curves represent the set of *Hopf* bifurcation points (---), that of $\rho_P = 0$ (-·-·-), and that of $\rho_H = 0$ (---), respectively. In (a), these 3 curves coincide]. Five cases are examined: (a) $Q_H = Q_P = 1$; (b) $Q_H = Q_P = 0.9$; (c) $Q_H = Q_P = 0.01$; (d) $Q_H = 0.9$, $Q_P = 0.5$; (e) $Q_H = 0.1$, $Q_P = 0.01$. $\beta = 0.5$ for (a)–(d) and $\beta = 1$ for (e). Other parameters: $r = 1$, $K = 10$, $c_H = 0$, $c_P = 0$. There were 100 modifiers with evenly separated mutation rates from 0 to 1.0, in both host and parasite populations. Four/five trajectories with different initial conditions are plotted in each panel. Open arrows in the figures indicate the predicted directions of coevolutionary trajectory suggested by the sign of the selection gradients (see text). closed circle denotes the point at which all the trajectories converged (i.e. a pair of coevolutionarily stable mutation rates).

TABLE 1
The summary of numerical simulations of host–parasite mutation coevolution for various parameter values

	host no mut. $0 = \bar{\mu}_H^* < \bar{\mu}_P^*$	host lower mut. $0 < \bar{\mu}_H^* < \bar{\mu}_P^*$	para lower mut. $\bar{\mu}_H^* > \bar{\mu}_P^* > 0$	para no mut. $\bar{\mu}_H > \bar{\mu}_P^* = 0$
$\beta = 0.25, 0.5$	23 + 23	1 + 1	0	0
$\beta = 1.0, 2.0$	7 + 10	16 + 8	1 + 6	0

The coevolutionarily stable set of host and parasite mutation rates ($\bar{\mu}_H^*, \bar{\mu}_P^*$) observed in simulations are classified as in the column. Each numeral in the table represents the number of simulations that fell into each category (Left numeral in each cell represents the result for tightly linked modifier, $c_H = c_P = 0$; and right one represents the result for unlinked modifier, $c_H = c_P = 0.5$.) Recombination rates between the selected and the modifier loci are assumed to be the same between host and parasite, but both are either tightly linked $c_H = c_P = 0$ or unlinked $c_H = c_P = 0.5$. The costs of deleterious mutations are also assumed to be the same between host and parasite, but they vary as $Q_H = Q_P = 0.9$ or 0.1 or 0.01 . The intrinsic finite rate of growth of host $\exp(r)$ varies as $r = 0.25, 0.5, 1$, and 2 . There are therefore $2 \times 2 \times 3 \times 4 = 48$ different combinations of parameters for each row.

Result (a) is easy to understand. The effect of linkage (b) can be explained in terms of the speed of evolution (see Discussion). We do not think that result (c) has any biological importance, because in such cases host and parasite densities fluctuate so hard that they are likely to become extinct.

We can therefore conclude that, except when parasite mutation is disproportionately harmful than that of host [the case (a)], or when the parasite's recombination rate is much larger than the host's [the case (b)], the coevolutionary outcomes tend to be that parasite mutation rate evolves to a very high level even if most mutations are lethal; whereas, the host mutation rate is driven to zero.

Discussion

This paper examined the possibility that host and parasite mutation rates would escalate in evolution to escape from parasite genotypes and to pursue host genotypes. In the first model, we analysed the evolution of mutation rate in a single host species, assuming frequency-dependent selection that would be expected at a locus responsible for antagonistic epidemiological interaction. In the second model, we examined the coevolution of host and parasite mutation rates by modeling explicit epidemiological

processes and joint evolution of mutation modifiers. To derive (co-)evolutionarily stable mutation rate(s), we examined the evolutionary genetic stability of mutation modifiers that may be linked or unlinked to the selected locus. The results are summarized as follows:

(i) In a single species frequency-dependent selection model, the mutation rate continues to increase through modifier evolution, until the oscillation of the genotype frequency in the selected locus is suppressed completely.

(ii) Adding the effect of deleterious mutation makes the evolutionarily stable population polymorphic with discrete set of modifiers—ES population typically consists of two mutation modifiers with zero and extremely high mutation rates, and could consist of three or more with distinctly different effects for a sufficiently strong deleterious effects.

(iii) Linkage between modifier and selected loci does not affect the evolutionary results much, contrary to the previous results for the mutation/recombination modification in a temporally fluctuating environment.

The coevolution model extends some of the above results, but reveals new characteristics of interspecific arms races. Gene-for-gene epidemiological interaction causes genotype densities and frequencies

TABLE 2
Effect of differential mutational risks

	host to mut. $0 = \bar{\mu}_H^* < \bar{\mu}_P^*$	host lower mut. $0 < \bar{\mu}_H^* < \bar{\mu}_P^*$	para lower mut. $\bar{\mu}_H^* > \bar{\mu}_P^* > 0$	para no mut. $\bar{\mu}_H > \bar{\mu}_P^* = 0$
$Q_H < Q_P$	24 + 24	0	0	0
$Q_H = Q_P$	23 + 23	1 + 1	0	0
$Q_H > Q_P$	9 + 10	0 + 1	0 + 1	15 + 12

Columns: the same as in Table 1. The left numeral in each cell is the result for $c_H = c_P = 0$, and right numeral is for $c_H = c_P = 0.5$. $r = 0.25, 0.5, 1$, or 2 . β is either 0.25 or 0.5 . Q_H and Q_P are the same and $0.01, 0.1$, or 0.9 . The results are classified according to their order into each row.

TABLE 3
Effect of differential linkages

	host no mut. $0 = \bar{\mu}_H^* < \bar{\mu}_P^*$	host lower mut. $0 < \bar{\mu}_H^* < \bar{\mu}_P^*$	para lower mut. $\bar{\mu}_H^* > \bar{\mu}_P^* > 0$	para no mut. $\bar{\mu}_H^* > \bar{\mu}_P^* = 0$
$c_H > c_P$	24 + 22	0 + 6	0	0
$c_H = c_P$	46 + 17	2 + 25	0 + 6	0
$c_H < c_P$	18 + 5	1 + 0	1 + 17	4 + 2

Columns: the same as in Table 1 and 2. In each cell, left numeral represent the results for $\beta = 0.25, 0.5$; and a right numeral, that for $\beta = 1.0, 2.0$. The fractions of successful mutations of host Q_H and parasite Q_P are assumed to be the same, but the values vary as $Q_H = Q_P = 0.9, 0.1$ and 0.01 . $r = 0.25, 0.5, 1$, or 2 . c_H and c_P are the same and are 0.0 (completely linked) or 0.5 (completely unlinked). The results are classified according to their order into each row.

cycles indefinitely in both host and parasite. This cycle occurs whenever host and parasite mutation rates are sufficiently small. The joint evolution of mutation modifiers then leads to the following outcome:

(iv) In the absence of deleterious effect of mutation, both host and parasite mutation rates are accelerated by the joint evolution of mutation modifiers, and reach a curve of equilibria on which genotype densities come to be stabilized by high mutation rates.

(v) Adding a small effect of deleterious mutation radically changes the conclusion—mutation rate evolves to zero in one species (typically host) and it evolves to a very high level in the other species (parasite). Coevolutionarily stable mutation rate of parasite can be very high even if most mutations are lethal. These results can be summarized as that parasite’s selective advantage for higher mutation rate will still exceed the costs of lethal mutations, when host mutation rate stops escalation by the excess of mutational load.

(vi) Using the same set of parameter values that leads to the asymmetrical coevolutionary equilibrium described above, but now that the parasite mutation rate is fixed at a low level, then host mutation rate is

evolutionarily escalated to a very high level. Thus, the host mutation rate is driven to zero, not by the cost of lethal mutations by itself, but by a highly mutable parasite.

Our assertion that the host tends to retreat from the arms race in mutation modifications could be compared with the general consensus on arms races between different classes (Dawkins & Krebs, 1979; Parker, 1983; Maynard Smith & Brown, 1986). In interspecific arms races, it has been suggested based on verbal argument that the species with a lower cost per unit investment, under more intense selection, with a faster rate of evolution, and of more specialized dependence will keep the other ahead in the arms level (Dawkins & Krebs, 1979). This general conjecture seems to fit to our results: (1) Parasite is more specialized than host in gene-for-gene interaction assumed here (based on the Nicholson–Bailey model): A parasite cannot increase at all in the absence of the specific host genotypes while for a host the “only” detrimental effect of a parasite is to reduce the growth rate of host. Thus, applying a life-dinner principle in this case, “the parasite mutates more frequently than the host, because the parasite is mutating for his life while the host is only mutating for his health.” This is the reason why the host retreats from the arms race if other conditions, which will be discussed below, are the same. (2) If the cost of deleterious mutation is considerably higher (smaller Q) in one species than in the other, then the species with a lower cost evolves to a high mutation rate. (3) If the modifier locus in one species is more loosely linked to the selected locus than in the other species, the one with looser linkage tends to lose the race, because the modifiers respond to selection in the primary locus less effectively in that species.

If the life-dinner principle is the main cause for the evolutionary retreats of host, it would depend on the specific epidemiological dynamics assumed. Gene-for-gene interactions are often modeled as density-independent matching-genotype games (Bell &

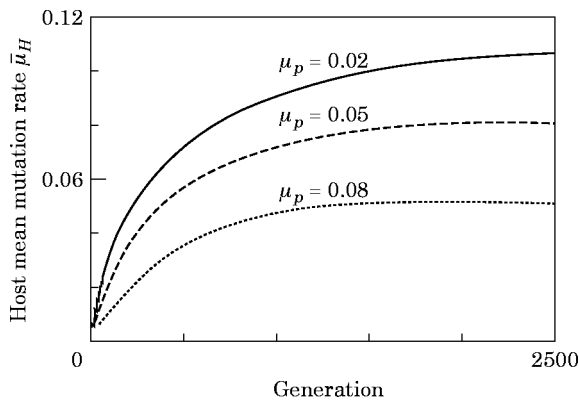


FIG. 9. The evolution of host mutation rates if the parasite mutation rate is fixed at $\mu_P = 0.02, \mu_P = 0.05$, and $\mu_P = 0.08$. Other parameters are the same as in Fig. 8(b), in which case the host mutation rate was driven to zero.

Maynard Smith, 1987; Seger & Hamilton, 1988; Nee, 1989). In such models, the degree of specific dependence to the other species can be similar in host and parasite, and then there may be no such general tendency that host mutation rate declines to zero through modifier coevolution.

Bell & Maynard Smith (1987) have shown in their “quantitative” model of host–parasite coevolution in recombination modifiers that a lower recombination is favored in host and a higher recombination is favored in parasite. At a glance this result seems similar to ours (host mutation rate evolves to zero while parasite mutation rate evolves to high), but the underlying mechanisms are by no means different. Indeed, their “gene-for-gene” model that is closer to ours has shown no such tendency that parasite recombination rate increases and host’s recombination rate decreases.

In single species frequency-dependent selection model with the effect of deleterious mutations, we predict that the evolutionarily stable population should consist of multiple modifiers with distinctly different effects, even though we allowed a continuum of modifiers with arbitrary effects to invade. This constitutes another example that the evolution may lead to a coalition of alleles that jointly refuse the invasion of any others (Brown & Vincent, 1987; Ludwig & Levin, 1991; Ellner & Hairston, 1994). That the evolutionarily stable population consists of a discrete set of genotypes, though only supported by numerical simulations in the present model, can be compared with the general theoretical results that an evolutionarily stable population consists of discrete phenotypes/genotypes (Sasaki & Ellner, 1995; Ellner & Sasaki, 1996).

More specifically, we predict that the evolutionarily stable population is typically dimorphic with a zero mutation modifier and a high mutation modifier. A dimorphic ESS is found in the model of the evolution of dispersal types in random environments (Levin *et al.*, 1984; Cohen & Levin, 1991; Ludwig & Levin, 1991).

Frequency-dependent selection favoring rare types tends to increase the number of alleles in the population. Our model reveals that if the selected locus is highly polymorphic, the selection for a higher mutation rate is less likely to occur. This might suggest that the evolution of a high mutation modifier under the frequency dependent selection (together with coexisting zero mutation modifier in general) would be applicable only when the selected locus segregates a few alleles. However, in a finite population, the allele frequency randomly fluctuates around the stable isopleth equilibrium and can be

lost from the population. This random fluctuation of genotype frequency would produce the selective advantage for a higher mutation rate even if there are infinitely many potential alleles in the selected locus. Supporting evidence was given by Gillespie (1981): he examined the mutation modification in a heterotic locus in a finite population. If the population is infinite, allele frequency should converge to an internal equilibrium and there must be no selective force for or against increased mutation rate. However, analyses of a diffusion process for modifier dynamics in a finite population showed that the selection always favors a modifier with a higher mutation rate in symmetric or nearly symmetric fitness schemes (Gillespie, 1981).

The trajectory and the endpoint of evolutionary games in general should depend on the specific genetic background of modifiers e.g. the number of modifier loci, the number of potential alleles in a modifier locus, linkage between modifier locus and selected locus. To predict the evolutionary outcome, we therefore combined the game-theoretical concept of coevolutionary stability and population genetics, by examining the invasibility of a mutant in a given modifier dynamics [This is called the evolutionary genetic stability (EGS) by Eshel & Feldman (1982)]. Numerical simulations of modifier dynamics suggested that the above approach gives an accurate prediction.

Additional biological conditions seem to strengthen our conclusion that the host tends to retreat from the mutation rate arms race: generation times of host and parasite may be different by several orders of magnitude. If the parasite has a much shorter life cycle than the host, the rate of modifier evolution would be faster in the parasite, thus favoring high mutation rate in the parasite and zero mutation rate in the host. Unequal genome sizes between host and parasite have a similar effect: as exemplified by viruses and their vertebrate hosts, genome sizes could be different between hosts and parasites by orders of magnitude. If a host has a much longer genome than a parasite, then the fraction of genes that are responsible for the gene-for-gene interaction in the whole genome should be much smaller for the host than that for the parasite. This again favors high mutation rate in the parasite and zero mutation rate in the host.

Gene-for-gene interaction between host and parasite genotypes has been proposed to describe epidemiological interactions between plants and their pathogens (Flor, 1956). More and more evidences have been accumulated supporting that many plant–pathogen relations fall into this category. There

are also an increasing number of theoretical studies that assumes gene-for-gene interaction in modeling coevolution of host and parasite [see Parker (1994) for references], many of which also assume that pathogen genotypes are narrowly specialized to host resistance genotypes. Recently Parker (1994) questioned the robustness of the theoretical conclusions derived from these models, by arguing that under empirically reasonable degree of differential genotypic specificity in virulence, sustained cycles of genotype frequencies are less likely to occur, which is the key for many theoretical predictions (e.g. the evolution of sex). However, it is very likely that we are missing many factors that tend to destabilize genotype dynamics (e.g. density-dependence in genotype dynamics, strong nonlinearity in frequency dependence, fluctuation due to environmental or demographic stochasticity and so on), as well as factors that tend to stabilize it (e.g. uneven specificity). We clearly need more detailed observation of the time series data before drawing any conclusive judgment for the ubiquity of cycles in gene-for-gene interactions.

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APPENDIX A

In this appendix, we show that a mutation modifier can always invade the population if and only if it produces a higher mutation rate than the wild type. Denote the mutation rate of mutant modifier by $\mu' = \mu + \Delta\mu$, where μ is the mutation rate specified by the wild type modifier. The invasibility of the mutant, if the marginal logarithmic growth rate (7) of mutant is positive. If mutant modifier is rare the A-allele-frequency in the wild type and in the mutant population (x_t^* and y_t^* respectively) after the selection stage are:

$$x_t^* = \frac{w(x_t)x_t}{\bar{w}_0} \quad \text{with}$$

$$\bar{w}_0 = w(x_t)x_t + w(1-x_t)(1-x_t), \quad (\text{A.1a})$$

$$y_i^* = \frac{w(x_i)y_i}{\bar{w}_1} \quad \text{with} \quad \bar{w}_1 = w(x_i)y_i + w(1-x_i)(1-y_i). \quad (\text{A.1b})$$

The frequencies in the next generation are then

$$x_{i+1} = (1-\mu)x_i^* + \mu(1-x_i^*), \quad (\text{A.2a})$$

$$y_{i+1} = (1-\mu-\Delta\mu)y_i^* + (\mu+\Delta\mu)(1-y_i^*). \quad (\text{A.2b})$$

Let $\xi_i^* = y_i^* - x_i^*$ be the difference in the frequencies of A alleles in M_1 and M_0 population after selection. Then from (A.1),

$$\xi_i^* = \frac{w(x_i)y_i}{\bar{w}_1} - \frac{w(x_i)x_i}{\bar{w}_0} = \frac{w(x_i)w(1-x_i)(y_i-x_i)}{\bar{w}_0\bar{w}_1}. \quad (\text{A.3})$$

Therefore, the allele frequency difference in the next generation $\xi_{i+1} = y_{i+1} - x_{i+1}$ is given by

$$\begin{aligned} \xi_{i+1} &= (1-2\mu)(y_i^* - x_i^*)\Delta\mu(1-2y_i^*) \\ &= (1-2\mu) \frac{w(x_i)w(1-x_i)}{\bar{w}_0\bar{w}_1} \xi_i + \Delta\mu(1-2y_i^*). \end{aligned} \quad (\text{A.4})$$

Because, the dynamics converges to a 2-periodic cycle taking two states symmetric around $1/2$, we must have $\xi_{i+1} = -\xi_i$ after the initial transient. Substituting this into (A.4) and rearranging it, we have

$$\left[1 + (1-2\mu) \frac{w(x_i)w(1-x_i)}{\bar{w}_0\bar{w}_1} \right] \xi_i = \Delta\mu(2y_i^* - 1). \quad (\text{A.5})$$

Suppose that $\Delta\mu > 0$ and $\mu < 1/2$. Then (A.5) states that ξ_i and $2y_i^* - 1$ must have the same sign. If we assume $\xi_i > 0$, then $y_i^* > 1/2$. It is clear from the assumption $\mu < 1/2$ that the mutation does not reverse the abundance order of allele frequencies, so that the A allele must still dominate the α allele frequency in M_1 population after mutation: $y_{i+1} > 1/2$. Since $\xi_{i+1} = y_{i+1} - x_{i+1}$ must be negative if ξ_i is positive, we have $x_{i+1} > y_{i+1}$ and hence $x_{i+1} > 1/2$. This in turn implies that $x_i < 1/2$ because x_i is fluctuating around $1/2$ with period 2. Thus, we proved that if $y_i > x_i$ then $x_i < 1/2$ and, by symmetrical argument, if $y_i < x_i$ then $x_i > 1/2$, after x_i and y_i converges to stable two-point cycles. Therefore we conclude that $\{w(x_i) - w(1-x_i)\}(y_i - x_i)$ becomes positive for all the generations of $\Delta\mu > 0$. This implies that a mutant modifier having larger mutation rate than the resident's can always invade the population.

APPENDIX B

In this appendix, we derive the optimal mutation rate which maximized the geometric mean fitness of the population, under strong selection. Suppose that $\mu < \mu_c$ so that the system converges to a two point cycle around $1/2$. So we set the frequency of the A allele be $x_i = 1/2 + z_i$. The population mean fitness is then

$$\bar{w}_i = e^{-\beta/2} f(z_i), \quad \text{with } f(z) = (1/2 + z)e^{-\beta z} + (1/2 - z)e^{\beta z}. \quad (\text{B.1})$$

On the other hand, z in the next generation is

$$z_{i+1} = \frac{1}{2}(1-2\mu) \frac{g(z_i)}{f(z_i)} \quad \text{with } g(z) = (1/2 + z)e^{-\beta z} - (1/2 - z)e^{\beta z}. \quad (\text{B.2})$$

As $\beta \rightarrow \infty$, $g(z_i)/f(z_i)$ approaches to -1 if $z_i > 0$ and approaches to 1 if $z_i < 0$. Hence in the limit of strong selection, the dynamics (B.2) can be approximated by

$$z_{i+1} = \begin{cases} \mu - 1/2 & \text{if } z_i > 0 \\ 1/2 - \mu & \text{if } z_i < 0. \end{cases} \quad (\text{B.3})$$

We then have the geometric mean fitness of the population:

$$\begin{aligned} GMF(\bar{w}_i) &= \sqrt{w_i w_{i+1}} \\ &= e^{-\beta/2} \{ \mu e^{\beta/2 - \beta\mu} + (1-\mu)e^{-\beta/2 + \beta\mu} \}. \end{aligned} \quad (\text{B.4})$$

As $\beta \rightarrow \infty$, (B.4) approaches to $\mu \exp(-\beta\mu)$, which is maximized at $\mu = 1/\beta$. This gives the optimal mutation rate of strong selection limit.

APPENDIX C

Stability of Nicholson–Bailey Gene-for-Gene System

In this section, we consider the local stability of the symmetric internal equilibrium state, $H_i = \hat{H}$, $P_i = \hat{P}$ of (15) and (16). The equilibrium is calculated by

$$\begin{aligned} \sigma_H \cdot r(1 - 2\hat{H}/K)e^{-\beta\hat{P}} - 1 &= 0, \\ \sigma_P \cdot \hat{H}(1 - e^{-\beta\hat{P}}) - \hat{P} &= 0. \end{aligned} \quad (\text{C.1})$$

where $\sigma_H = 1 - \mu_H + Q_H\mu_H$ and $\sigma_P = 1 - \mu_P + Q_P\mu_P$. Jacobian matrix of the system (15) and (16) at the equilibrium is given by

$$\mathbf{M} = \begin{bmatrix} a_1 & a_2 & b_1 & b_2 \\ a_2 & a_1 & b_2 & b_1 \\ c_1 & c_2 & d_1 & d_2 \\ c_2 & c_1 & d_2 & d_1 \end{bmatrix} \quad (\text{C.2})$$

with

$$\begin{aligned} a_1 &= \frac{(1 - \mu_H)}{\sigma_H} - \frac{r}{K} \hat{H}, & a_2 &= \frac{Q_H \mu_H}{\sigma_H} - \frac{r}{K} \hat{H}, \\ b_1 &= -\frac{(1 - \mu_H)}{\sigma_H} \beta \hat{H}, & b_2 &= -\frac{Q_H \mu_H}{\sigma_H} \beta \hat{H} \\ c_1 &= \frac{(1 - \mu_P)}{\sigma_P} \frac{\hat{P}}{\hat{H}}, & c_2 &= \frac{Q_P \mu_P}{\sigma_P} \frac{\hat{P}}{\hat{H}} \\ d_1 &= (1 - \mu_P) \beta \hat{H} e^{-\beta \hat{P}}, & d_2 &= Q_P \mu_P \beta \hat{H} e^{-\beta \hat{P}}. \end{aligned}$$

The equilibrium $(\hat{H}, \hat{H}, \hat{P}, \hat{P})$ is locally stable if all the eigenvalues of \mathbf{M} have an absolute value of less than one. From (C.2), we can decompose the characteristic equation for \mathbf{M} as

$$\begin{aligned} \lambda^2 - (a_1 + a_2 + d_1 + d_2)\lambda + (a_1 + a_2)(d_1 + d_2) \\ - (b_1 + b_2)(c_1 + c_2) = 0 \end{aligned} \quad (\text{C.3a})$$

$$\begin{aligned} \lambda^2 - (a_1 - a_2 + d_1 - d_2)\lambda + (a_1 - a_2)(d_1 - d_2) \\ - (b_1 - b_2)(c_1 - c_2) = 0. \end{aligned} \quad (\text{C.3b})$$

The eigenvalues from (C.3a) correspond to the dynamics for the total host and total parasite densities, and the eigenvalues from (C.3b) correspond to the dynamics for the difference $H_A - H_a$ and $P_A - P_a$. *Hopf* bifurcation occurs when

$$\begin{aligned} (a_1 - a_2)(d_1 - d_2) - (b_1 - b_2)(c_1 - c_2) \\ = \frac{\delta_H \delta_P}{\sigma_H \sigma_P} \left\{ \beta \hat{P} + \beta \hat{H} \sigma_P e^{-\beta \hat{P}} \right\} = 1 \end{aligned} \quad (\text{C.4a})$$

or

$$\begin{aligned} (a_1 + a_2)(d_1 + d_2) - (b_1 + b_2)(c_1 + c_2) \\ = \beta \hat{P} + \beta \hat{H} \sigma_P e^{-\beta \hat{P}} \left\{ 1 - r \frac{2\hat{H}}{K} \right\} = 1 \end{aligned} \quad (\text{C.4b})$$

where (C.4a) and (C.4b) respectively correspond to the characteristic eqns (C.3a) and (C.3b). (C.4a) and (C.1) define the curve in $\mu_H - \mu_P$ plane, on which *Hopf* bifurcation occurs.