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Mutating away from your enemies: The evolution of mutation rate in a host–parasite system

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ABSTRACT

The rate at which mutations occur in nature is itself under natural selection. While a general reduction of mutation rates is advantageous for species inhabiting constant environments, higher mutation rates can be advantageous for those inhabiting fluctuating environments that impose on-going directional selection. Analogously, species involved in antagonistic co-evolutionary arms races, such as hosts and parasites, can also benefit from higher mutation rates. We use modifier theory, combined with simulations, to investigate the evolution of mutation rate in such a host–parasite system. We derive an expression for the evolutionary stable mutation rate between two alleles, each of whose fitness depends on the current genetic composition of the other species. Recombination has been shown to weaken the strength of selection acting on mutation modifiers, and accordingly, we find that the evolutionarily attracting mutation rate is lower when recombination between the selected and the modifier locus is high. Cyclical dynamics are potentially commonplace for loci governing antagonistic species interactions. We characterize the parameter space where such cyclical dynamics occur and show that the evolution of large mutation rates tends to inhibit cycling and thus eliminates further selection on modifiers of the mutation rate. We then find using computer simulations that stochastic fluctuations in finite populations can increase the size of the region where cycles occur, creating selection for higher mutation rates. We finally use simulations to investigate the model behaviour when there are more than two alleles, finding that the region where cycling occurs becomes smaller and the evolutionarily attracting mutation rate lower when there are more alleles.

1. Introduction

Mutation is the fundamental source of genetic variation, without which adaptation could not occur. The rate at which mutations occur has, therefore, been of long-standing interest to evolutionary biologists (Muller, 1928; Mukai, 1964; Drake et al., 1998). The notion that mutation rates themselves are subject to natural selection has been well documented empirically (Sniegowski et al., 1997, 2000; Baer et al., 2007). It would seem at first that there should be a strong selective pressure to eliminate mutation altogether, due to the high probability that any particular mutation will have deleterious effects. This general reduction principle has been shown to hold in theoretical models pioneered by Sam Karlin and colleagues (Karlin and McGregor, 1974; Liberman and Feldman, 1986) for populations at equilibrium in non-changing environments, where there is no cost to increased replication fidelity. However, when higher replication fidelity entails a cost (due to, for example, increased energy allocation during transcription), then selection favours an intermediate mutation rate that balances the fitness cost associated with deleterious mutations and the energy savings associated with a higher mutation rate (André and Godelle, 2006).

While reducing mutation rates is evolutionarily favoured in a constant environment, were it not for costs, the same is not true in a novel environment. In a novel environment a mutator lineage (one with a higher mutation rate) still carries the burden of an increased deleterious mutation load. However, it now also has a higher probability of experiencing a beneficial mutation. When such a beneficial mutation occurs in a mutator lineage it can pull the mutator allele to a higher frequency (a mechanism referred to as genetic hitch-hiking; Maynard-Smith and Haigh, 1974). The above ideas have been confirmed in a number of theoretical models (Kimura, 1967; Leigh, 1970; Johnson, 1999).

Because modifiers of the mutation rate are primarily subject to indirect selection via their effects at other loci (the cost of replication fidelity being the exception to this rule), modifier dynamics are highly sensitive to their rate of recombination with the target loci that are the subject of both mutation and direct selection. Recombination has been shown to weaken the strength

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of indirect selection acting on mutation modifiers (Kimura, 1967; Leigh, 1970; Sniegowski et al., 1997). This can be understood as follows. Suppose a beneficial mutant arises in a mutator lineage. With a high enough recombination rate, it is probable that the beneficial allele will recombine into the non-mutator lineage during its spread. In this way the mutator lineage "shares" the benefits of the beneficial mutants it creates. Meanwhile deleterious mutations will accumulate on the mutator background more rapidly than on the non-mutator background. While recombination allows some of these mutator lineages to escape the deleterious effects of their mutations, a large number of mutator lineages will be eliminated by purifying selection before any recombination occurs. Consequently, because beneficial mutations have a longer sojourn time within a population, on average, than deleterious mutations, the benefits of producing beneficial mutations are dissipated over time by recombination, while the costs of producing deleterious mutations are more immediately felt. This intuitive argument has been considered explicitly in models of directional selection (Johnson, 1999).

A novel environment is not the only scenario that has been shown to be capable of selecting for higher mutation rates. For example, a number of theoretical models have shown that increased mutation rates can be advantageous in fluctuating environments, where the direction of selection periodically changes (see Leigh, 1970, 1973; Ishii et al., 1989). In this situation individuals are repeatedly under pressure to adapt. Antagonistic co-evolutionary interactions, such as those that occur between hosts and parasites, can also create selection for increased mutation rates. Because adaptive changes in one species often have detrimental effects on the other, hosts and parasites repeatedly create "novel" environments for one another (this is commonly referred to as the "Red Queen" hypothesis; Van Valen, 1973). With host–parasite interactions, it has been shown that mean fitness is optimized by high or non-zero mutation rates, in a manner similar to that found with fluctuating abiotic environments (Nee, 1989; Sasaki, 1994; Haraguchi and Sasaki, 1996). There is also empirical evidence that host–parasite co-evolution can favour increased mutation rates. For example, Pal et al. (2007) recently found that co-evolution with viruses drove up the mutation rates in the bacterium *Pseudomonas fluorescens*.

Host–parasite interactions are commonly mediated through antigen molecules, which are expressed on the surface of parasite cells. For hosts, a pathogen's antigen molecule provides a useful target to aid in its detection and thus elimination. Consequently, hosts have evolved sophisticated mechanisms enabling them to detect and respond to a wide array of possible antigen types, while parasites have evolved complex mechanisms allowing them to regularly produce offspring with antigens differing from their own. This process of "antigen switching" in parasites has been well documented empirically (Brannan et al., 1994; Turner, 1997; Frank, 2002), and consequently many of the mechanisms that have evolved in order to make the process more efficient are now well understood. A good summary of many of these is available in Frank (2002). Frank describes, for example, the process of "gene conversion", whereby some parasites can copy one of several non-expressed archival antigen alleles into a single expressed site. In this way they are able to store many variant antigen alleles in their genome, while only ever expressing a single one. Because each mutant is drawn from a pool of alleles that have been historically exposed to selection, switching in this way is more likely than random mutation to produce viable mutants. Such a strategy can be found in *Trypanosoma brucei*, which causes "sleeping sickness" in several African mammals. This particular parasite has been shown to carry hundreds of alternative loci in its genome (Pays and Nolan, 1998). For discussions of similar mechanisms see also Donelson (1995) (in *Borrelia hermsii*); Svard et al. (1998) (in *Giardia lamblia*); Kusch and Schmidt (2001) (in free-living protozoa).

In a theoretical model of host–parasite co-evolution using mean fitness arguments, Nee (1989) found that antagonistic interactions can lead to an indefinite escalation of mutation rates in both species, provided that the selection induced by these interactions is strong relative to mutation rates. Haraguchi and Sasaki (1996) later extended this model to consider the effects of deleterious mutations and found that only a small amount of unconditionally deleterious mutation was sufficient to prevent the above reported indefinite escalation of mutation rates.

Like Haraguchi and Sasaki (1996), we consider a modifier extension to the model introduced in Nee (1989). Unlike Haraguchi and Sasaki (1996), however, we allow recombination to occur between the mutation modifier and the selected locus. We find that, under certain conditions, this addition results in a qualitatively different outcome, with recombination acting to reduce the evolutionarily attracting mutation rate by distributing the benefits of advantageous mutations. We closely follow the methods of Gandon and Otto (2007), who analyzed a modifier of the rate of recombination between two loci mediating host–parasite interactions. We supplement our analytical model with computer simulations, which allow us to investigate extensions to finite populations, as well as to more alleles.

2. Methods and results

2.1. Model description

We consider two co-evolving haploid species: a host and a parasite. We follow haplotype frequencies through a life cycle consisting of a census, selection, and reproduction. Mating is random within each species, and (except where noted) population sizes are assumed constant and large enough that drift can be ignored. Antagonistic interactions between species are mediated through a single locus in hosts and a single locus in parasites, each with two alleles (A_h/a_h in hosts and A_p/a_p in parasites). A second locus in each species determines the rate of mutation between A_i and a_i, where the forward and backward mutation rates are assumed equal. Throughout i denotes the species type: h for hosts, p for parasites. We denote the two alleles at this mutator locus by M_i and m_i. The four haplotypes within a species are thus $\{a_im_i, a_iM_i, A_im_i, A_iM_i\}$. We let $x_{i,j}$ denote the frequency of the jth genotype in species i (labelled in the order given above).

Fitness is determined by a matching-alleles model, introduced by Hamilton (1980). Specifically, when the host genotype matches that of the parasite (e.g., A_p parasite and A_h host, or a_p parasite and a_h host), the parasite experiences a fitness increase of $\alpha_p > 0$ and the host a fitness decrease of $\alpha_h < 0$. The fitness of the jth genotype in species i is then given by

$$w_{i,j} = 1 + \alpha_i(\zeta_j(x_{\bar{i},1} + x_{\bar{i},2}) + (1 - \zeta_j)(x_{\bar{i},3} + x_{\bar{i},4})) \tag{1}$$

where ζ_j is equal to 1 for $j \in \{1, 2\}$ and 0 for $j \in \{3, 4\}$ and where an overbar denotes the other species type ($\bar{h} = p$, $\bar{p} = h$). If $\mu_{i,M}$ ($\mu_{i,m}$) is the probability that mutation occurs at the A-locus in an individual of species i carrying the M_i (m_i) allele at the M-locus (with $\mu_{i,m}$ and $\mu_{i,M}$ both $\leq 1/2$), then the frequencies after selection and mutation, but before sex and recombination, are given by

$$\begin{aligned}
x'_{i,1} &= (1 - \mu_{i,m})(w_{i,1}/\bar{w}_i)x_{i,1} + \mu_{i,m}(w_{i,3}/\bar{w}_i)x_{i,3} \\
x'_{i,2} &= (1 - \mu_{i,M})(w_{i,2}/\bar{w}_i)x_{i,2} + \mu_{i,M}(w_{i,4}/\bar{w}_i)x_{i,4} \\
x'_{i,3} &= (1 - \mu_{i,m})(w_{i,3}/\bar{w}_i)x_{i,3} + \mu_{i,m}(w_{i,1}/\bar{w}_i)x_{i,1} \\
x'_{i,4} &= (1 - \mu_{i,M})(w_{i,4}/\bar{w}_i)x_{i,4} + \mu_{i,M}(w_{i,2}/\bar{w}_i)x_{i,2}
\end{aligned} \tag{2}$$

where $\bar{w}_i$ (the mean fitness of species i) is given by

$$\bar{w}_i = \sum_{j=1}^{4} w_{i,j}x_{i,j}.$$

In the text, we assume that the modifier allele only alters the mutation rate at the A-locus, but in Appendix A we also include a cost to the modifier of producing unconditionally deleterious alleles. Letting ψ_i denote the product of the probability that a haploid individual engages in sexual reproduction and the probability of recombination between the A and the M loci in species i, the genotype frequencies after sex and recombination are given by

$$\begin{aligned} x''_{i,1} &= x'_{i,1} - \psi_i D'_i \\ x''_{i,2} &= x'_{i,2} + \psi_i D'_i \\ x''_{i,3} &= x'_{i,3} + \psi_i D'_i \\ x''_{i,4} &= x'_{i,4} - \psi_i D'_i \end{aligned} \tag{3}$$

where D'_i denotes the linkage disequilibrium in species i after mutation and selection. It can be computed as $D'_i = x'_{i,1}x'_{i,4} - x'_{i,2}x'_{i,3}$.

Denoting the frequency of A by $p_{i,A}$, and the frequency of M by $p_{i,M}$, we have

$$\begin{aligned} p_{i,A} &= x_{i,3} + x_{i,4} \\ p_{i,M} &= x_{i,2} + x_{i,4}. \end{aligned} \tag{4}$$

In the matching-alleles model, allele frequencies typically fluctuate around 1/2 over time. The key simplification that we make is that these fluctuations are relatively small, so that the allele frequencies remain near 1/2. If we define $\delta_{i,A}$ as the departure of the frequency of the A allele from 1/2, so that $\delta_{i,A} = (x_{i,3} + x_{i,4}) - 1/2$, we may then convert the recursion equations described in Eq. (3) into a new system of recursion equations involving $\delta_{i,A}$, $p_{i,M}$, and D_i.

Assuming that $\delta_{i,A}$ is small, specifically that it is of the order of a small term ϵ, and that the modifier also has a small effect on the mutation rate, such that $\mu_{i,M} - \mu_{i,m}$ is also of order ϵ, we find that disequilibrium rapidly evolves to a level that is of order ϵ^2 (see Appendix B for details). With the above assumptions it is possible to simplify the recursion for $\delta_{i,A}$. Up to order ϵ we get

$$\begin{pmatrix} \delta_{h,A}[t+1] \\ \delta_{p,A}[t+1] \end{pmatrix} = \mathbb{M} \begin{pmatrix} \delta_{h,A}[t] \\ \delta_{p,A}[t] \end{pmatrix} \tag{5}$$

where

$$\mathbb{M} = \begin{pmatrix} (1-2\mu_{h,M}) & \dfrac{\alpha_h}{(2+\alpha_h)}(1-2\mu_{h,M}) \\ \dfrac{\alpha_p}{(2+\alpha_p)}(1-2\mu_{p,M}) & (1-2\mu_{p,M}) \end{pmatrix}.$$

While this approach requires that disequilibrium is small (order ϵ^2), it is not necessary that it remains at the steady state values predicted by the current state of the population, as is the case in a quasi-linkage equilibrium analysis (for more information on quasi-linkage equilibrium analyses see Barton, 1995). Thus Eq. (5) can be applied even when selection is large relative to the rates of sex and recombination.

The point $\delta_{h,A} = \delta_{p,A} = 0$ is an equilibrium of Eq. (5), as well as of the full recursion equations. A local stability analysis shows that this point is unstable with complex eigenvalues as long as

$$\begin{aligned} R &= \sqrt{\det(\mathbb{M})} \\ &= \sqrt{(1-2\mu_{p,M})(1-2\mu_{h,M})\frac{(1+\alpha_p/2+\alpha_h/2)}{(1+\alpha_p/2)(1+\alpha_h/2)}} \end{aligned} \tag{6}$$

is greater than one, where $\det(\mathbb{M})$ is the determinant of the matrix $\mathbb{M}$ and R is the magnitude of the leading eigenvalue of $\mathbb{M}$.

When R is greater than one, the frequencies in a species cycle sinusoidally outwards with time. However, when R is near one the cycles remain small for extended periods of time. Without loss of generality we let $t = 0$ denote the time at which the allele frequency in the host first passes 1/2 (equivalently $\delta_{h,A}$ first passes zero). This allows us to express the general solution to (5), after simplifying, as

$$\delta_{h,A}[t] = R^{t-1}(1-2\mu_{h,M})\frac{\alpha_h}{(\alpha_h+2)}\frac{\sin[\phi t]}{\sin[\phi]}\delta_{p,A}[0] \tag{7a}$$

$$\begin{aligned} &\delta_{p,A}[t] \\ &\quad = R^{t-1}\sqrt{R^2-(1-2\mu_{h,M})(1-2\mu_{p,M})}\frac{\sin[\phi t+\sigma]}{\sin[\phi]}\delta_{p,A}[0] \end{aligned} \tag{7b}$$

where ϕ denotes the speed of evolutionary cycles (the period is $2\pi/\phi$), and σ is the phase difference between the host and parasite cycles:

$$\phi = \cos^{-1}\left[\frac{(1-\mu_{p,M}-\mu_{h,M})}{R}\right] \tag{8a}$$

$$\sigma = \cos^{-1}\left[\frac{\mu_{p,M}-\mu_{h,M}}{\sqrt{R^2-(1-2\mu_{p,M})(1-2\mu_{h,M})}}\right]. \tag{8b}$$

The asymmetry between (7a) and (7b) is a consequence of our starting time when $\delta_{h,A}[0] = 0$.

Recalling that $\alpha_h < 0$ and $\alpha_p > 0$, it can be shown that R increases with the strength of selection (magnitude of α_i). Thus, we can see from Eq. (8a) that the cycle period decreases as selection becomes stronger in either species. This is illustrated in Fig. 1. Similarly, the period decreases as $\mu_{i,M}$ (the mutation rate) increases in either species.

Fig. 2 shows how the phase difference between host and parasite cycles (σ) depends on the mutation rates in the two species. Our results qualitatively confirm those of Nee (1989). When the mutation rates are equal the two species cycle 90° out of phase, regardless of the strength of selection in either species (see Eq. (8b)). When the hosts have a higher mutation rate the cycles are $>$ 90° out of phase, and when the parasites have a higher mutation rate they are $<$ 90° out of phase. If all else is equal, the phase difference σ is larger when selection is weak. This is because changes in one species take longer to induce a response in the other species. Interestingly, in this model only small deviations from 90° are possible in the parameter region where cycling occurs ($R > 1$), as indicated by the small range of the y-axis in Fig. 2. Nee (1989) argued that large phase shifts cannot occur, because they require that at some point in each cycle one of the two species evolves away from the currently favoured allele. For the parameters investigated here (e.g., those in Fig. 1) the phase

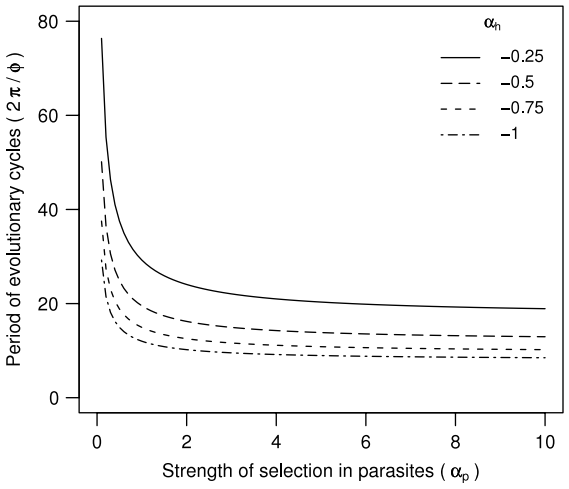

Fig. 1. Period of co-evolutionary cycles (in generations) as a function of the strength of selection in parasites. Other parameters were $\mu_{h,M} = \mu_{p,M} = 1 \times 10^{-3}$ per generation.

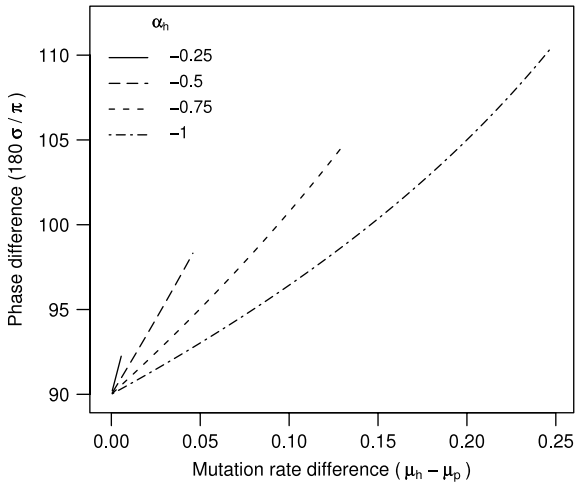

Fig. 2. Phase difference (in degrees) between host and parasite cycles as a function of the difference in their per generation mutation rates. Other parameters were $\mu_{p,M} = 1 \times 10^{-3}$ and $\alpha_p = (1+\alpha_h)^{-1} - 1$ (for each curve). Curves are only plotted where $R > 1$.

difference from a 90° shift is always less than what would result from a single generation of evolution in the wrong direction. Thus, the phase differences from 90° that occur in this model result from slight overshooting based on allele frequencies from the previous generation.

Having described the dynamics of the selected locus, we turn now to the dynamics of the modifier locus. After selection and sexual reproduction, the change in frequency of the modifier allele is exactly given by

$$\Delta p_{i,M}[t] = p_{i,M}[t+1] - p_{i,M}[t] = \frac{4D_i[t]\alpha_i\delta_{\bar{i},A}[t]}{2+\alpha_i(1+4\delta_{i,A}[t]\delta_{\bar{i},A}[t])}. \quad (9)$$

This is analogous to Eq. (29a) in Gandon and Otto (2007). In Appendix B, we solve for the disequilibrium in species i. We show that when $\delta_{i,A}$ is assumed small (of order ϵ), the effect of the mutation rate modifier is assumed weak (of order ϵ), and the disequilibrium in the previous generation (D_i) has reached order ϵ^2, the general solution for the disequilibrium is

$$D_i[t] = 2(1-\psi_i)(\mu_{i,m}-\mu_{i,M})(1-p_{i,M})p_{i,M} \times \sum_{\tau=1}^{t} X_i^{\tau-1}\left(\delta_{i,A}[t-\tau] + \frac{\alpha_i}{(\alpha_i+2)}\delta_{\bar{i},A}[t-\tau]\right) \quad (10)$$

where $X_i = (1-\psi_i)(1-2\mu_{i,M})$ and the influence of the initial conditions is assumed to have dissipated. Substituting (10) into (9) yields

$$\Delta p_{i,M} = \frac{8\alpha_i(1-\psi_i)(\mu_{i,m}-\mu_{i,M})(1-p_{i,M})p_{i,M}\delta_{\bar{i},A}[t]}{2+\alpha_i(1+4\delta_{i,A}[t]\delta_{\bar{i},A}[t])} \times \sum_{\tau=1}^{t} X_i^{\tau-1}\left(\delta_{i,A}[t-\tau] + \frac{\alpha_i}{(\alpha_i+2)}\delta_{\bar{i},A}[t-\tau]\right) \quad (11)$$

which is the analogue for a mutation modifier of Eq. (33) for the recombination modifier in Gandon and Otto (2007). Because $X_i < 1$ whenever there is some sex/recombination or mutation, the sum may be evaluated explicitly using Eq. (7). We can then average the change in modifier allele frequency over one co-evolutionary cycle, ignoring transient dynamics due to the initial conditions. We also average over all possible starting points in the host–parasite cycle. Doing so, we find that the modifier allele M that increases the mutation rate in species i spreads whenever the following is positive:

$$\text{sign}[\,\overline{\Delta p_{i,M}}\,] \simeq \text{sign}[c_1 X_i(1-\mu_{\bar{i},M}-\mu_{i,M})/2 - (\mu_{\bar{i},M}-\mu_{i,M})(X_i-(1-2\mu_{\bar{i},M}))], \quad (12)$$

where c_1 is the positive constant $-\alpha_h\alpha_p/(2+\alpha_h+\alpha_p)$. The first term in Eq. (12) is always positive and thus always favours higher mutation rates. It is largest when sex/recombination is rare (small ψ_i and large X_i) and when selection is strong (large c_1). We may re-write Eq. (12) as

$$\text{sign}[\,\overline{\Delta p_{i,M}}\,] \simeq \text{sign}[(R^2-(1-2\mu_{i,M})(1-\mu_{i,M}-\mu_{\bar{i},M}))X_i + R^2(\mu_{\bar{i},M}-\mu_{i,M})] \quad (13)$$

in order to facilitate interpretation. Because $R > 1$ when there are cycles, the first term must be positive. It tends to dominate when linkage is tight (X_i large) and when the mutation rates are similar (second term small). Conditioning upon the existence of cycles ($R > 1$), Eq. (13) can become negative and favour lower mutation rates only when $\mu_{i,M}$ is sufficiently greater than $\mu_{\bar{i},M}$. It follows that selection will tend to increase the mutation rate in a species, unless that mutation rate is substantially higher than the mutation rate in the other species. This creates a "ratcheting-up" effect, where an increase in the mutation rate in one species creates selection for a corresponding increase in the other species.

2.2. Evolutionarily attracting mutation rate

Assuming that the mutation rates start small, we expect, based on our reasoning above, that they will increase until the second term in Eq. (13) becomes negative. Thus setting Eq. (13) (or equivalently Eq. (12)) equal to zero allows us to find the evolutionarily attracting level of mutation (μ_i^*), for a given mutation rate in the other species. Defining the positive constants

$$c_{2,i} = \frac{c_1}{2-c_1}\left(1+\frac{1}{2(1-\psi_i)}\right) + \frac{\psi_i}{2(1-\psi_i)}$$

allows us to simplify μ_i^*, giving

$$\mu_i^* = \mu_{\bar{i},M} + (1/2-\mu_{\bar{i},M})\left(-c_{2,i} + \sqrt{c_{2,i}^2 + 2\left(\frac{c_1}{2-c_1}\right)}\right). \quad (14)$$

As the terms in parentheses are positive, Eq. (14) shows that the evolutionarily attracting mutation rate is higher than that of the antagonistic species. Fig. 3 plots the evolutionarily attracting mutation rate in hosts (solid line) as a function of the strength of selection in parasites (left panels) and in hosts (right panels). The shaded region indicates where cycling ceases ($R < 1$) and thus where selection on mutation modifiers becomes neutral. We expect populations with low initial mutation rates to evolve until they reach μ_i^*, or until mutation rates become large enough that cycles at the selected locus disappear ($R \leq 1$). In Fig. 3, therefore, we would expect population mutation rates starting at or near zero to proceed upwards until they reach the minimum of the black line or the border of the grey region.

2.3. Different generation times

A main assumption in our model is that the host and parasite generation times are equal. We relaxed this assumption using two methods (described in more detail in Appendix C). In both cases we varied the host generation time, while assuming the parasite dynamics to be governed by the same equations as in the main text. We first assumed that all hosts were subject to selection and mutation at each time step, but that only a subset of the

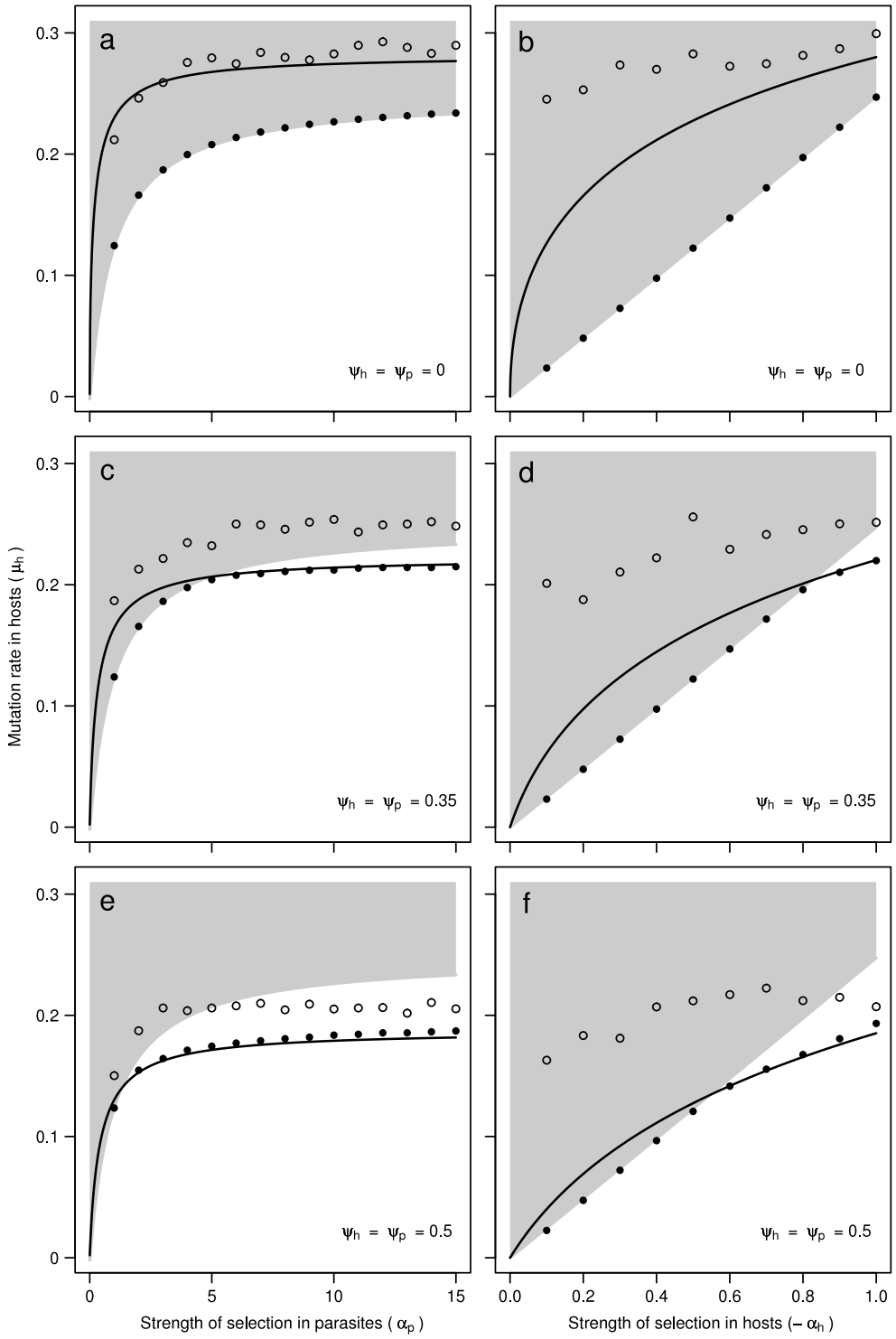

Fig. 3. Evolutionarily attracting per generation mutation rate in hosts as a function of the strength of selection in parasites (a, c, e) and in hosts (b, d, f). The rate at which sex and recombination (ψ_i) occurs is given in each panel. Solid black lines denote the predicted mutation rate corresponding to Eq. (14) and shaded regions indicate where cycling does not occur ($R < 1$). $\alpha_h = -1$ in panels a, c, e, and $\alpha_p = 100$ in panels b, d, f. Filled and open circles correspond to simulations with population sizes of 10^9 and 10^3 (in both hosts and parasites), respectively. μ_p was 0.002 in all panels (results are very similar unless $\mu_p \gg 0$). Evolved mutation rates in hosts are the mean of 50 replicate runs, each of which was averaged over the last 5×10^6 of 10^7 generations.

individuals reproduced sexually. We then changed the assumption that all individuals were subject to mutation at each time step, and assumed instead that mutations only occurred when individuals reproduced sexually. In both cases we found that, when hosts lived longer, the evolutionarily attracting mutation rate in hosts was higher than it was when the generation times were equal. This is because individuals who live longer undergo less recombination per unit time, and thus remain linked to the beneficial mutations they produce for more time steps (see Introduction).

2.4. One-species model

To help understand the effects of the speed versus the amplitude of evolutionary cycles we considered a simplified

one-species model where selection fluctuated deterministically over time (see Appendix D). We found that the speed of cycles was important in deciding whether a modifier of the mutation rate was selected for or against (see Eq. (D.4)), with faster cycles selecting for higher mutation rates. In contrast to the results of our two-species model, however, a one-species model revealed that the strength of selection at the selected locus only affected the strength of selection at the modifier locus, not the direction of selection. This qualitative difference occurs as a result of the dependence of the cycle speed (ϕ) on the selection strength (α_h and α_p) in the two-species model, whereas in the one-species model the cycle speed is fixed. As in the two-species model, we also find that higher recombination rates reduce the evolutionary attracting mutation rate in the one-species model.

2.5. Numerical simulations

We ran computer simulations to investigate separately the effects of two additional factors: drift in finite populations, and more than two alleles at the selected locus. We considered a Wright–Fisher model with constant population size. Each generation consisted of selection followed by recombination and then mutation. Host–parasite interactions were governed by the same fitness matrix as was used in the analytical model. The mutation rate was first allowed to evolve in only one species at a time. While it is theoretically clearer this way, it may also be biologically realistic in the case where one of the species is more constrained in its ability to modify mutation rates. All individuals in the evolving population were initialized with mutation rates equal to zero. A single novel mutator allele was introduced at the M-locus in a randomly drawn individual whenever fixation at that locus occurred. The mutation rate of the novel mutator was drawn from a Gaussian distribution centered at the current population mean and with a standard deviation of 0.01 (negative mutation rates were set to 0). All simulations were run for 10^7 generations.

For very large populations (10^9 individuals in each species), where drift is negligible, the simulations matched up perfectly with analytical predictions (see the solid black points in Fig. 3). In smaller populations (1000 individuals in each species), however, stochastic fluctuations in allele frequency created additional opportunities that favoured the evolution of higher mutation rates (for example, by creating fluctuations when cycles would not be expected based on analytical predictions). Thus, for small populations higher mutation rates evolved (see the open circles in Fig. 3).

We also used simulations to investigate the effects of higher numbers of alleles at the selected locus. With k possible alleles at the selected locus, mutation was set so that an allele of type i had a uniform probability of mutating to any of the other $k-1$ types. There was a significant reduction in the size of the region in which cycling occurred with more alleles (see Fig. 4), and where cycling did occur, the period was longer. The combination of these two changes led to an overall reduction in the evolutionarily attracting mutation rate. However, the dependence on the strength of selection and recombination exhibited qualitatively similar results to those for the two-allele case. For example, in Fig. 4a high recombination causes a reduction in the evolutionarily attracting mutation rate into the region where cycles persist.

Finally, we investigated co-evolution between hosts and parasites by allowing the mutation rates to evolve simultaneously in both species. As before, a single novel mutator allele was introduced into either host or parasite populations when either became monomorphic at the mutation rate locus. We focused on the two-allele case at the locus mediating species interactions. When the populations were large, escalation of mutation rates in both species led to the eventual cessation of cycles, at which point evolution stopped (Fig. 5a). As before, however, when the populations were small stochastic fluctuations drove the mutation rates to higher values than expected, based on our analytical model (Fig. 5b). When the strength of selection differed between the species, the mutation rates rose to higher levels in the species with the larger selection coefficient. In essence, the species with more at stake kept ahead in the co-evolutionary arms race (Fig. 5).

3. Discussion

We have used analytical and simulation models to investigate the evolution of mutation rate in a co-evolving host–parasite system. In order to maintain consistency with other similar articles we have based our models on the matching-alleles model of host–parasite interactions, where each host allele can be matched by one parasite allele (whether matching causes infection or resistance is immaterial in the haploid two-allele model because we are free to define the alleles such that A_p parasites are able to infect A_h hosts; Otto and Michalakis (1998)). We followed the host and parasite populations over multiple generations, where interactions between the two species occurred at random at each time step.

We derived an expression for the evolutionary attracting mutation rate between two alleles, each of whose fitness was dependent on the current genetic composition of the other co-evolving species (see Eq. (14)). We found, in accordance with previous literature for directional selection (Kimura, 1967; Leigh, 1970; Sniegowski et al., 1997), that lower mutation rates are expected to evolve with higher levels of recombination (Fig. 3).

In order to account for the higher number of deleterious mutations that often accompany increased mutation rates, several authors have imposed additional fitness costs on individuals with higher mutation rates (Sasaki, 1994; Haraguchi and Sasaki, 1996). In our model individuals with a higher mutation rate suffer a fitness cost at certain points in the cycle through their elevated probability of mutating from the more fit to the less fit allele. However, to maintain consistency with other authors, we also considered a general cost to increased mutation rates (see Appendix A). We found, not surprisingly, that higher costs reduced the evolutionarily attracting mutation rate.

Because an imbalance in allele frequencies in one species creates selection for an imbalance in the opposite direction in the other species, cyclical fluctuations can occur at the selected locus. When these fluctuations are absent, allele frequencies at the selected locus converge to a stable polymorphism, at which point selection at the mutation rate locus disappears. We characterized the parameter space in which cycling does or does not occur (see the non-shaded and shaded regions in Figs. 3 and 4) and showed that large mutation rates can inhibit cycling (a result previously shown by both Seger 1988 and Nee 1989). We, therefore, expect that evolution will lead populations with initially small mutation rates to our predicted evolutionarily attracting mutation rate (μ_i^* from Eq. (14)) or until the point where cycles disappear, should this occur first. This prediction was tested with computer simulations, which confirmed our expectations when the population sizes were very large (see the solid circles in Fig. 3). However, when the population sizes were small, higher than expected mutation rates evolved. Drift in small populations can create stochastic fluctuations in allele frequencies (Seger and Hamilton, 1988). Such fluctuations extend the region where selection on a modifier occurs, accounting for an increased evolutionarily attracting mutation rate.

From Figs. 3 and 4, it is apparent that the evolutionarily attracting mutation rate predicted in our model, when interpreted as a "per site" mutation rate, is extraordinarily high. When viewed as an antigenic "switching rate", or a "per trait" mutation rate,

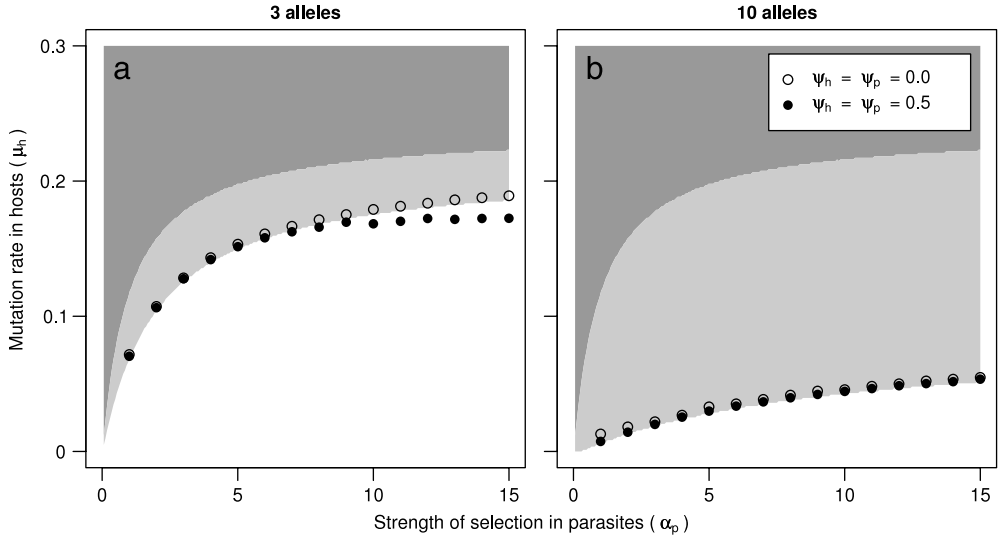

Fig. 4. Evolutionarily attracting per generation mutation rate in hosts with multiple alleles at the selected locus. The shaded light grey regions indicate where cycling did not occur in the three-allele (panel a) and ten-allele (panel b) model, and the shaded dark grey region indicates where cycling did not occur in the two-allele model and is included for reference. Shaded regions were generated using simulations; cycling was considered absent whenever the allele frequency range over the last 500 generations of the simulations fell below 0.005. With two alleles, this region corresponded well to the region where $R < 1$. For the large population sizes used here (10^9 hosts and 10^9 parasites), a clear transition from cycling to no cycling occurs. Recombination rates were set to 0.5 (filled circles) and 0 (open circles), $\alpha_h = -1$, and $\mu_p = 0.002$. Each point is the mean of 10 replicate runs, each of which was averaged over the last 5×10^6 of 10^7 generations.

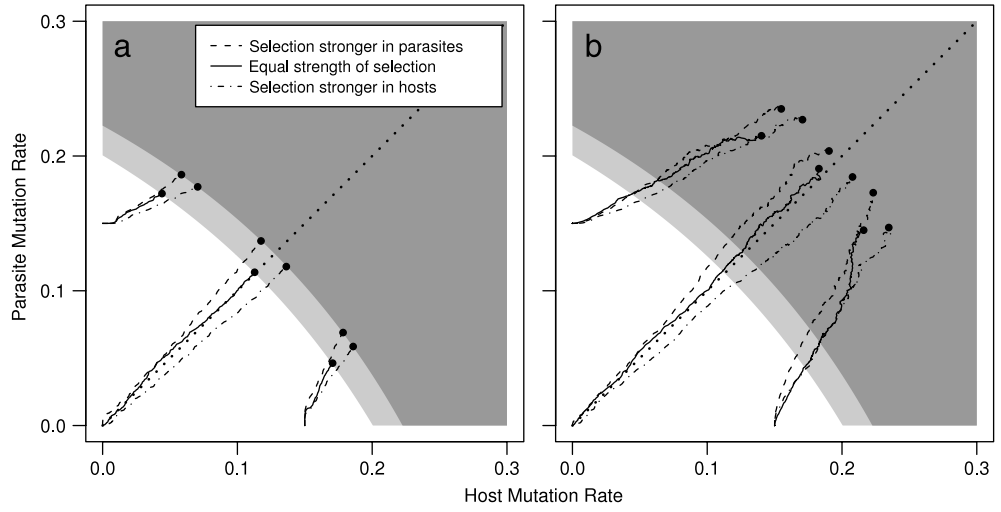

Fig. 5. Co-evolutionarily trajectories in simulations with differing strengths of selection in hosts and parasites. Each curve represents the mean of 100 replicate runs. Initial mutation rates were either 0 in both hosts and parasites, 0 in hosts and 0.15 in parasites, or 0.15 in hosts and 0 in parasites. Points represent final values after 10^7 generations. The light shaded regions indicate where cycles are not expected in the analytical model ($R < 1$) for $\alpha_h = -0.9$, $\alpha_p = 9$ and the dark shaded regions indicate where cycles are not expected for both $\alpha_h = -0.9$, $\alpha_p = 99$ and $\alpha_h = -0.99$, $\alpha_p = 9$. Population sizes in both hosts and parasites were 10^9 in (a) and 10^4 in (b). When the strength of selection was equal in both species we used $\alpha_h = -0.9$ and $\alpha_p = 9$; when selection was stronger in the parasites we used $\alpha_h = -0.9$ and $\alpha_p = 99$; finally, when selection was stronger in the hosts we used $\alpha_h = -0.99$ and $\alpha_p = 9$. The dotted line has a slope of one and is included for reference. Recombination rates were set to 0.

however, it is not as unrealistic and is consistent with theoretically predicted switching rates for parasites based on *within host* dynamics (Sasaki, 1994). By not including an explicit cost to high mutation rates in the text, we have implicitly assumed that the modifier has a very localized effect on the mutation rate at the locus mediating the host–parasite interaction. While mutation rates can be highly site specific (Frank, 2002), it is likely that mutation rate modification is an intricate process, and therefore probable that modifiers of the mutation rate will have pleiotropic deleterious effects. Accounting for this in our model by including additional costs reduced the predicted mutation rate toward which the system evolved (see Appendix A), as was the case in both Sasaki (1994) and Johnson (1999). It is also possible that very high mutation rates would be evolutionarily favoured at loci that mediate host–parasite interactions, but that such high rates take a long time to evolve (or may not evolve at all because of genetic constraints), so that real populations may not have reached such high levels.

A major assumption in our analytical model is that there are only two possible alleles at the selected locus. Seger (1988) has shown that the dynamics can differ qualitatively with multiple alleles. We, therefore, used computer simulations to investigate more than two alleles. We found that the evolutionarily attracting mutation rate decreased, and in accordance with Seger (1988), the region where cycling occurred became smaller with more alleles (see Fig. 4). As in the case for two alleles, the mutation rates did not always evolve simply to the point where cycles stopped. This can be seen by comparing points in Fig. 4a and observing that when selection is strong and recombination is high the evolutionarily attracting mutation rate lies in the region where

cycling persists. Because hosts and parasites usually have a large number of potential beneficial alleles (Frank, 2002), we would predict, based on the above, that most real populations would exhibit much lower mutation rates than those predicted by a two-allele model.

Factors that led to longer cycles decreased the evolutionarily attracting mutation rate. Cycles were longer when selection was weak in either species (see Fig. 1), when the difference between host and parasite mutation rates was large (see Eq. (8a)), and when there were more alleles (results not shown). Because cycles in one species create a fluctuating selective pressure in the other species, the observed decrease in the evolutionarily attracting mutation rate with each of the above factors is consistent with previous findings that in fluctuating environments the optimal mutation rate is proportional to the inverse of the length of selective episodes (Leigh, 1970, 1973; Ishii et al., 1989).

When cycles persisted in our model, we observed that hosts and parasites were usually very close to 90° out of phase. This is consistent with the results of Nee (1989), who argued that large deviations from 90° cannot be sustained, because they would require one of the two species to regularly evolve in the "wrong" direction. While, in our model, the phase shift σ can theoretically range from to 0° to 180°, we found that cycles disappear well before σ becomes too different from 90° and large deviations were, therefore, never observed (see Fig. 2). For large population sizes, cycles also never appeared drastically more or less than 90° out of phase in our simulations. However, in small populations, where cycles were largely driven by genetic drift, large phase shifts were observed (not shown), as was also noted by Gandon and Nuismer (2009) for a spatially structured population.

For a wide range of parameters, cycles were ephemeral, disappearing once the mutation rates had evolved to sufficiently high levels (see Fig. 3). Furthermore, the range of parameters where cycles persist became smaller as the number of alleles increased (see Fig. 4). These findings question the legitimacy of the pervasive assumption that loci governing host–parasite interactions exhibit cyclical dynamics. A lack of empirical evidence for recurrent cycles further questions this assumption's legitimacy. To our knowledge, there is only a single empirical study that presents data supporting cyclical dynamics (i.e. changes in allele frequency which eventually return to the same value; several additional studies show change consistent with either cycles or directional selective sweeps). Stahl et al. (1999) used coalescence theory to argue that a 9.8 million year old polymorphism for disease resistance in *Arabidopsis thaliana* must have been maintained by frequency-dependent selection, and furthermore, showed signs of having historically differed in frequency. While consistent with cycling, their results are also consistent with an alternative explanation; a recent change in the environment could have altered the relative fitness cost of the resistance allele, resulting in a shift in allele frequencies. More long-term empirical data are, therefore, needed to determine whether true cycles occur in host–parasite systems.

Acknowledgments

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Appendix A. Cost of deleterious mutations

Here we modify the model by including an explicit cost to modifiers that increase the mutation rate. This cost reflects the assumption that mutators will suffer from a higher load of unconditionally deleterious mutations at sites other than the *A*-locus. Rather than model these other sites explicitly, we incorporate a cost $C_i\mu_i$ of having a mutation rate of μ_i. Technically this is equivalent if the unconditionally deleterious mutations are lethal. To incorporate costs of producing unconditionally deleterious mutations we add the following step between mutation/selection (Eq. (2)) and sex/recombination (Eq. (3)).

$$\begin{aligned}
x''_{i,1} &= (1 - C_i\mu_{i,m})/\bar{C}_i\, x'_{i,1}\\
x''_{i,2} &= (1 - C_i\mu_{i,M})/\bar{C}_i\, x'_{i,2}\\
x''_{i,3} &= (1 - C_i\mu_{i,m})/\bar{C}_i\, x'_{i,3}\\
x''_{i,4} &= (1 - C_i\mu_{i,M})/\bar{C}_i\, x'_{i,4}\\
\bar{C}_i &= 1 - C_i\mu_{i,m}(x'_{i,1} + x'_{i,3}) - C_i\mu_{i,M}(x'_{i,2} + x'_{i,4}).
\end{aligned} \tag{A.1}$$

A mutation modifier M that increases the mutation rate by $(\mu_{i,M} - \mu_{i,m})$ will experience a reduction in frequency each time step that is proportional to $C_i(\mu_{i,M} - \mu_{i,m})$. In order that costs do not dominate dynamics at the modifier locus (i.e., they are not so large as to drive all mutation rates to 0) we must assume that the C_i are of order ϵ^2, where ϵ is a small term, as discussed prior to Eq. (10). An analysis similar to that in the main text shows that a modifier that increases the mutation rate invades whenever the following is positive:

$$\begin{aligned}
\overline{\Delta p_{i,M}} = {} & c_3[c_1X_i(1 - \mu_{\bar{i},M} - \mu_{i,M})/2\\
& - (\mu_{\bar{i},M} - \mu_{i,M})(X_i - (1 - 2\mu_{\bar{i},M}))]\\
& - C_i(1 - p_{i,M})p_{i,M}(\mu_{i,M} - \mu_{i,m})
\end{aligned} \tag{A.2}$$

where c_3 is the positive constant

$$c_3 = \frac{(R^{\frac{4\pi}{\phi}} - 1)\phi \csc^2[\phi]\alpha_h^2(1 - \psi_i)(1 - p_{i,M})p_{i,M}(\mu_{i,M} - \mu_{i,m})(\delta_{p,A}[0])^2}{\pi \log[R](R^2 - 2\cos[\phi]X_iR + X_i^2)(\alpha_i + 2)^2(1 - 2\mu_{\bar{i},M})}. \tag{A.3}$$

Costs always select against higher mutation rates, but as long as the costs are sufficiently weak that Eq. (A.2) is positive when the mutation rate in a species is zero, then evolution will lead the system toward a non-zero level of mutation. The evolutionarily attracting mutation rate can be determined by setting $\overline{\Delta p_{i,M}}$ equal to 0 using Eq. (A.2) and numerically solving for μ_i.

We used simulations to investigate model behaviour when costs differed between hosts and parasites (see the main text for simulation methods). In accordance with Haraguchi and Sasaki (1996), we found that when the mutation rates were allowed to co-evolve from low initial values (zero in each species), populations experienced an initial phase of selection for high mutation rates followed by a subsequent phase of selection for decreased rates in the species bearing the higher costs (see the trajectories beginning at the origin in Fig. A.1). In contrast to Haraguchi and Sasaki (1996), however, the mutation rates in our model remained at non-zero values in both species (convergence toward equilibrium values occurred from both directions; Fig. A.1). Furthermore, unlike Haraguchi and Sasaki (1996), we did not observe any asymmetries between hosts and parasites. This is because parasite populations did not require hosts for their survival in our model, whereas in the model of Haraguchi and Sasaki (1996), parasite survival was dependent on their ability to find a host. Consequently, Haraguchi and Sasaki (1996) find that it is more often the hosts that tend to retreat towards a zero mutation rate, due to their having less at stake.

Interestingly, we did not observe a large effect of population size when costs were included (compare left and right panels of Fig. A.1). Because sufficiently large costs can outweigh any indirect benefits to mutation rate modifiers, selection for higher mutation

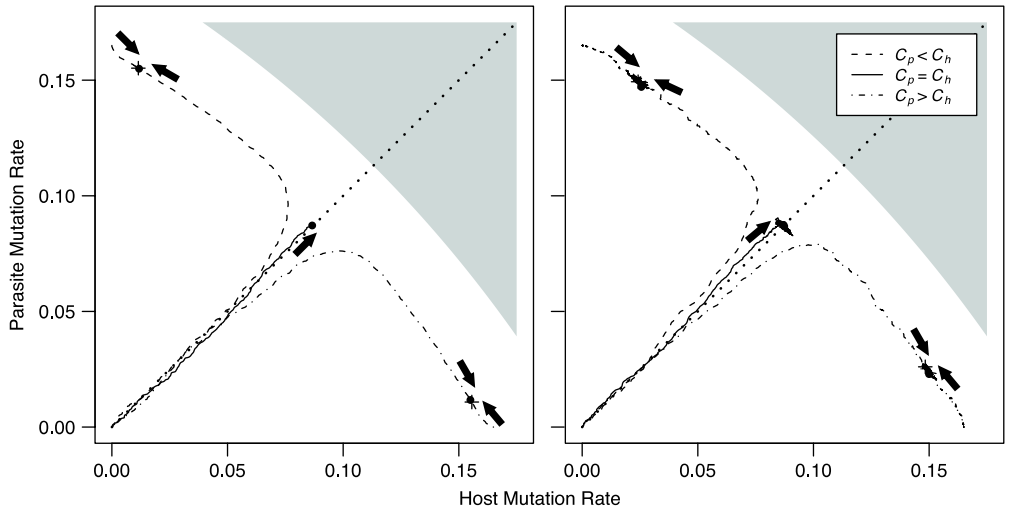

Fig. A.1. Co-evolutionarily trajectories in simulations with differing costs associated with mutation rate modifiers. Each curve represents the mean of 100 replicate runs. Solid points represent final values after 10^7 generations for trajectories initialized with both host and parasite mutation rates set to 0 and + symbols represent final values for populations initialized with mutation rates of 0 in hosts and 0.165 in parasites, or 0.165 in hosts and 0 in parasites. The shaded region indicates where cycles are not expected in the analytical model ($R < 1$). Population sizes were 10^9 (left panel) and 10^3 (right panel) in both hosts and parasites. When the costs were equal we used $C_h = C_p = 0.5$ and when they differed we used $C_h = 0.25$, $C_p = 0.5$ and $C_h = 0.5$, $C_p = 0.25$. The dotted line has a slope of one and is included for reference. Recombination rates were set to 0, α_h to -0.9, and α_p to $1/(1+\alpha_h) - 1$ (so that the strength of selection was the same in both species). The parameters in this figure are identical to those in Fig. 5 with $\alpha_h = -0.9$ and $\alpha_p = 9$, except for the addition of costs of mutation.

rates is likely to disappear while rates are still low enough to permit co-evolutionary cycling (as was the case for the parameters presented in Fig. A.1). When this happens, the added indirect benefits created by stochastic allele frequency fluctuations in small populations have only a small effect and thus do not significantly change the final outcome of co-evolution.

Appendix B. Solving the recursion equations for the disequilibrium

Here we derive recursion equations for the disequilibrium in species i. By definition,

$$D_i'' = x_{i,1}'' x_{i,4}'' - x_{i,2}'' x_{i,3}''.$$

We can then use Eqs. (2) and (3) to write D_i'' in terms of genotype frequencies from the previous generation. Making the following substitutions

$$\begin{aligned}
x_{i,1} &= 1/2\,(1-p_{i,M})(1-2\delta_{i,A}) + D_i \\
x_{i,2} &= 1/2\,p_{i,M}(1-2\delta_{i,A}) - D_i \\
x_{i,3} &= 1/2\,(1-p_{i,M})(1+2\delta_{i,A}) - D_i \\
x_{i,4} &= 1/2\,p_{i,M}(1+2\delta_{i,A}) + D_i
\end{aligned}$$

gives us a recursion equation for D_i.

We next assume that $\delta_{i,A}$ is small (specifically of the order of a small term ϵ) and that the mutation rate modifier has a small effect (i.e. $\mu_{i,M} - \mu_{i,m}$ is also of order ϵ). A simple analysis of the first three terms in the Taylor series of D_i (taken with respect to ϵ) shows that the $\mathcal{O}(\epsilon^2)$ term is the first that could possibly grow in a single generation (both the $\mathcal{O}(1)$ and $\mathcal{O}(\epsilon)$ terms only decay by a factor proportional to $X_i = (1-\psi_i)(1-2\mu_{i,M})$). It follows that any initial disequilibrium in the system will rapidly evolve to a level that is at most of order ϵ^2. We, therefore, make the assumption that disequilibrium is already of this order in order to avoid any transient effects of initial conditions. Our recursion equation for D_i can then be simplified to

$$\begin{aligned}
D_i[t] = (1-\psi_i)\Big[&(1-2\mu_{i,M})D_i[t-1] \\
&+ 2p_{i,M}(1-p_{i,M})(\mu_{i,m}-\mu_{i,M}) \\
&\times \left(\delta_{i,A}[t-1] + \frac{\alpha_i}{(\alpha_i+2)}\delta_{\bar{i},A}[t-1]\right)\Big] + O(\epsilon^3).
\end{aligned}$$

We assume that enough time has passed that the initial disequilibrium $D_i[0]$ exerts negligible influence. With this assumption we can solve the above recursion equation to get

$$\begin{aligned}
D_i[t] &= 2(1-\psi_i)(\mu_{i,m}-\mu_{i,M})(1-p_{i,M})p_{i,M} \\
&\times \sum_{\tau=1}^{t}((1-\psi_i)(1-2\mu_{i,M}))^{\tau-1} \\
&\times \left(\delta_{i,A}[t-\tau] + \frac{\alpha_i}{(\alpha_i+2)}\delta_{\bar{i},A}[t-\tau]\right) + O(\epsilon^3).
\end{aligned}$$

Appendix C. Different generation times

Here we relax the assumption made in the main text that the host and parasite generation times are equal. We assume that the parasite dynamics remain exactly as they are in the main text, and then vary the generation times in hosts in two ways.

In the first model we assume that all hosts are subject to mutation and selection at every time step, but that only a proportion g takes part in sexual reproduction. This is incorporated by replacing Eq. (3) in the main text (for hosts only) with

$$\begin{aligned}
x_{h,1}'' &= (1-g)x_{h,1}' + g(x_{h,1}' - \psi_h D_h') = x_{h,1}' - g\psi_h D_h' \\
x_{h,2}'' &= (1-g)x_{h,2}' + g(x_{h,2}' + \psi_h D_h') = x_{h,2}' + g\psi_h D_h' \\
x_{h,3}'' &= (1-g)x_{h,3}' + g(x_{h,3}' + \psi_h D_h') = x_{h,3}' + g\psi_h D_h' \\
x_{h,4}'' &= (1-g)x_{h,4}' + g(x_{h,4}' - \psi_h D_h') = x_{h,4}' - g\psi_h D_h'.
\end{aligned} \tag{C.1}$$

It is clear from Eq. (C.1) that when $g = 1$ the model reduces to that presented in the main text. It is also clear that this modification effectively scales the recombination rates in hosts by the factor g. This has the net effect of reducing the recombination rate in hosts (by a factor g), which will ultimately increase the evolutionarily attracting mutation rate, provided it is predicted to lie within a region where cycles occur (see Fig. 3). Thus, increasing the host generation time (smaller g) results in hosts evolving a higher mutation rate.

In our second model we assume that all hosts are subject to selection every time step, but only a proportion g takes part in sexual reproduction, at which point mutation and recombination

occur. This can be incorporated by replacing our recurrence equation (3) in the main text (for hosts only) with

$$\begin{aligned} x'''_{h,1} &= (1-g)x'_{h,1} + g(x''_{h,1} - \psi_h D''_h) \\ x'''_{h,2} &= (1-g)x'_{h,2} + g(x''_{h,2} + \psi_h D''_h) \\ x'''_{h,3} &= (1-g)x'_{h,3} + g(x''_{h,3} + \psi_h D''_h) \\ x'''_{h,4} &= (1-g)x'_{h,4} + g(x''_{h,4} - \psi_h D''_h) \end{aligned} \tag{C.2}$$

where $x'_{h,j}$ denotes the frequency of genotype j after selection and $x''_{h,j}$ denotes the frequency of genotype j after selection *and* mutation. Again it is clear that when $g = 1$ our model reduces to that in the main text. A similar analysis to that in the main text then yields

$$\delta_{h,A}[t] = R^{t-1}(1-2g\mu_{h,M})\frac{\alpha_h}{(\alpha_h+2)}\frac{\sin[\phi t]}{\sin[\phi]}\delta_{p,A}[0]$$

$$\begin{aligned} &\delta_{p,A}[t] \\ &\quad = R^{t-1}\sqrt{R^2 - (1-2g\mu_{h,M})(1-2\mu_{p,M})}\frac{\sin[\phi t+\sigma]}{\sin[\phi]}\delta_{p,A}[0] \end{aligned}$$

where R, ϕ and σ are:

$$R = \sqrt{(1-2\mu_{p,M})(1-2g\mu_{h,M})\frac{(1+\alpha_p/2+\alpha_h/2)}{(1+\alpha_p/2)(1+\alpha_h/2)}}$$

$$\phi = \cos^{-1}\left[\frac{(1-\mu_{p,M}-g\mu_{h,M})}{R}\right]$$

$$\sigma = \cos^{-1}\left[\frac{\mu_{p,M}-g\mu_{h,M}}{\sqrt{R^2-(1-2\mu_{p,M})(1-2g\mu_{h,M})}}\right].$$

The recursion equation for $D_h[t]$ (Eq. (10)) also changes, becoming

$$\begin{aligned} D_h[t] &= 2(1-\psi_h)g(\mu_{h,m}-\mu_{h,M})(1-p_{h,M})p_{h,M} \\ &\quad \times \sum_{\tau=1}^{t} X_i^{\tau-1}\left(\delta_{h,A}[t-\tau] + \frac{\alpha_h}{(\alpha_h+2)}\delta_{p,A}[t-\tau]\right) \end{aligned}$$

where $X_h = 1 - g\psi_h - 2g\mu_{h,M} + 2g\mu_{h,M}\psi_h$.

An analysis following that in the main text shows that a modifier of the mutation rate in hosts can invade whenever the following is positive:

$$\begin{aligned} \text{sign}[\,\overline{\Delta p_{h,M}}\,] \simeq \text{sign}\big[&c_1 X_h(1-\mu_{p,M}-g\mu_{h,M})/2 \\ &+ (g\mu_{h,M}-\mu_{p,M})(X_h-(1-2\mu_{p,M}))\big] \end{aligned} \tag{C.3}$$

and in parasites

$$\begin{aligned} \text{sign}[\,\overline{\Delta p_{p,M}}\,] \simeq \text{sign}\big[&c_1 X_p(1-g\mu_{h,M}-\mu_{p,M})/2 \\ &+ (\mu_{p,M}-g\mu_{h,M})(X_p-(1-2g\mu_{h,M}))\big]. \end{aligned} \tag{C.4}$$

From the first of these equations, it can be seen that lengthening the generation time in hosts (reducing g) increases the relative importance of the first term in Eq. (C.3), which will tend to increase the evolutionarily attracting mutation rate in the host. The reverse is true in the parasite, where all else being equal a longer host generation time effectively reduces the host's mutation rate per unit time, which reduces selection for increased mutation rates in the parasite.

Appendix D. One-species model

Here we consider a simplified version of the model above where instead of two interacting species there is only a single species under a fluctuating selection regime. As before, we consider two loci, each with two alleles. The four possible haplotypes are then *am*, *aM*, *Am* and *AM*. We let x_j denote the frequency of the jth genotype (labelled in the order just given).

The A-locus is assumed to be under a fluctuating selection regime. That is, the fitness of genotype j in the t^{th} generation is given by

$$w_j[t] = \begin{cases} 1+\alpha\sin[\beta t] & \text{if } j = 1,2 \\ 1-\alpha\sin[\beta t] & \text{if } j = 3,4. \end{cases} \tag{D.1}$$

As in the two-species model we construct recursion equations, beginning with selection, then mutation, and finally sex and recombination. Performing a change of variables allows us to describe the system with recursions for the linkage disequilibrium ($D[t]$), the departure from a frequency of 0.5 at the A-locus ($\delta[t]$), and the frequency of the modifier ($p_M[t]$). In addition to the order assumptions made in the two-species model (see the main text preceding Eq. (5)), we must assume here that selection is also weak (α is on the order of ϵ; this assumption was not necessary in the two-species model, but there we assumed $\delta_{h,A}$ and $\delta_{p,A}$ were both small). It can then be shown in a similar manner to that in Appendix B that, transient initial effects aside, the disequilibrium will remain of order at most ϵ^2. With these assumptions we can find a general solution for $\delta[t]$ which, after simplification, is given by

$$\begin{aligned} &\delta[t+1] \\ &\quad = \frac{\alpha(1-2\mu_M)((1-2\mu_M)\sin[\beta t] - \sin(\beta[t-1]))}{4(2\mu_M^2 + (1-\cos[\beta])(1-2\mu_M))}. \end{aligned} \tag{D.2}$$

As in the two-species model we next find a general solution for the linkage disequilibrium ($D[t]$), again ignoring transient effects of the initial conditions. This can be simplified to

$$\begin{aligned} D[t] &= (1-\psi)(1-p_M)p_M(\mu_m-\mu_M) \\ &\quad \times \sum_{\tau=1}^{t}((1-\psi)(1-2\mu_M))^{\tau-1}(2\delta[t-\tau] \\ &\quad - \alpha\sin[\beta(t-\tau)]). \end{aligned} \tag{D.3}$$

Finally we consider the change in frequency of a mutation rate modifier, averaged over a complete selective cycle. The expected change per generation is then

$$\begin{aligned} E[\Delta p_M[t]] &\approx (1-\psi)(\mu_m-\mu_M)p_M(1-p_M) \\ &\quad \times \frac{\alpha^2(\cos[\beta](1+X\theta)-X-\theta)}{(1+X^2-2X\cos[\beta])(1+\theta^2-2\theta\cos[\beta])} \end{aligned} \tag{D.4}$$

where $\theta = (1-2\mu_M)$. It is apparent from Eq. (D.4) that the direction of selection on a modifier depends on the speed of evolutionary cycles (β), with faster cycles (larger β) selecting for higher mutation rates. In contrast to the two-species model, where the direction of selection was also dependent on the strength of selection (because the speed of evolutionary cycles ϕ contained both α_h and α_p), we find that the strength of selection, α, in the one-species model does not affect the sign of selection on a modifier, although it does affect the strength of indirect selection.

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