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THE COEVOLUTIONARY DYNAMICS OF ANTAGONISTIC INTERACTIONS MEDIATED BY QUANTITATIVE TRAITS WITH EVOLVING VARIANCES

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Abstract.—Quantitative traits frequently mediate coevolutionary interactions between predator and prey or parasite and host. Previous efforts to understand and predict the coevolutionary dynamics of these interactions have generally assumed that standing genetic variation is fixed or absent altogether. We develop a genetically explicit model of coevolution that bridges the gap between these approaches by allowing genetic variation itself to evolve. Analysis of this model shows that the evolution of genetic variance has important consequences for the dynamics and outcome of coevolution. Of particular importance is our demonstration that coevolutionary cycles can emerge in the absence of stabilizing selection, an outcome not possible in previous models of coevolution mediated by quantitative traits. Whether coevolutionary cycles evolve depends upon the strength of selection, the number of loci, and the rate of mutation in each of the interacting species. Our results also generate novel predictions for the expected sign and magnitude of linkage disequilibria in each species.

Key words.—Adaptive dynamics, coevolution, disequilbria, genetic variance, geographic mosaic, quasi-linkage equilibrium.

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Numerous interactions between species are mediated by quantitative traits. The susceptibility of many plants to insect herbivores, for instance, is determined by the concentration of defensive compounds in the plant and the activity of detoxifying enzymes in the insect (Berenbaum et al. 1986; Berenbaum and Zangerl 1998; Bergelson et al. 2001). Quantitative traits also mediate interactions between predators and prey (Benkman 1999; Brodie and Brodie 1999; Abrams 2000; Brodie et al. 2002), parasites and hosts (Soler et al. 2001; Kruger and Davies 2002), and pollinators and plants (Schemske and Horvitz 1989; Steiner and Whitehead 1991; O'Neil 1999; Galen and Cuba 2001; Alexandersson and Johnson 2002). Because quantitative traits play such a ubiquitous role in mediating interspecific interactions, they are likely to be of central importance to the coevolutionary process (Thompson 1999).

Efforts to understand the coevolutionary dynamics of interactions mediated by quantitative traits have taken both empirical and theoretical approaches. A critical contribution of empirical studies has been the measurement of the strength of reciprocal selection acting on quantitative traits of the interacting species (e.g., Berenbaum and Zangerl 1992; Benkman 1999; Clayton et al. 1999; Benkman et al. 2001). These studies have repeatedly demonstrated that the potential for coevolution mediated by quantitative traits is substantial. A limitation of these approaches is their focus on single geographic locations and points in time, generally precluding prediction of coevolutionary dynamics over broad spatial scales or time frames (Thompson 1999). Recent studies have attempted to move beyond these limitations by comparing traits of interacting species over broad geographic scales (Berenbaum and Zangerl 1998; Benkman et al. 2001; Brodie et al. 2002; Zangerl and Berenbaum 2003). Often these studies conclude that there is evidence for coevolutionary cycling or for a role of gene flow in generating local maladaptation (Thompson and Cunningham 2002; Zangerl and Berenbaum 2003). A major problem with critically evaluating results from these studies, however, is that we do not have clear theoretical expectations for the conditions that lead to coevolutionary cycling in even single isolated communities, let alone for sets of communities interconnected by gene flow (Bergelson et al. 2001).

So far, theoretical predictions for coevolutionary dynamics of interactions mediated by quantitative traits have almost exclusively been based on models making very specific assumptions about the structure of genetic variance. In fact, with respect to their genetic assumptions, the majority of models that have explicitly considered quantitative traits, rather than single loci, have fallen into one of two basic categories. The first category of models assumes that the genetic variances of the interacting species are fixed, which greatly simplifies mathematical analysis (e.g., Saloniemi 1993; Abrams and Matsuda 1997; Gavrilets 1997; Case and Taper 2000; Nuismer and Kirkpatrick 2003). In general, these models are simple extensions of the single-species approaches pioneered by Lande and others in the 1970s and 1980s (Lande 1976, 1979, 1981, 1982; Charlesworth 1993). The second category of models that has been profitably applied to the study of coevolutionary dynamics in predator-prey or host-parasite interactions is based on the theory of adaptive dynamics (e.g., Dieckmann and Law 1996; Metz et al. 1996; Geritz et al. 1998; Abrams 2001). Unlike the fixed genetic variance models, mathematical analysis of these adaptive dynamics models is made possible by assuming that standing genetic variance is absent. Thus, with the adaptive dynamics approach evolution proceeds only when genetic variation is transiently produced by new mutations. Although both categories of models have been invaluable as tools for achieving mathematical results, their divergent and apparently extreme genetic assumptions call into question the generality of their predictions. We know, for instance, that most quantitative traits do exhibit substantial standing genetic variation (Falconer and Mackay 1996) and that over evolutionary time scales this genetic variation can evolve (Steppan et al. 2002;

Whitlock et al. 2002; Begin and Roff 2003). What we do not know, however, is whether predictions based upon results from models using the two different assumptions differ qualitatively from each other or from other biologically plausible modeling scenarios in which standing genetic variation is allowed to evolve (Zhang et al. 2002; Barton and Turelli 2004; Jones et al. 2004).

Determining the extent to which the specific genetic assumptions of these divergent modeling approaches shape model predictions is an important goal of this paper. We are particularly interested in the conditions that allow coevolutionary cycles to evolve. Through slight modification of existing results, we first show that both adaptive dynamics and fixed genetic variance approaches predict that no cycling occurs in the absence of stabilizing selection. Using identical assumptions about the action of selection, we then develop a multilocus model of coevolutionary interactions that explicitly allows the genetic variances of the underlying quantitative traits to evolve. This multilocus model is analyzed using the moment-based approaches pioneered by Barton and Turelli (Turelli and Barton 1990; Barton and Turelli 1991; Kirkpatrick et al. 2002) in conjunction with genetically explicit multilocus simulations. Our analyses reveal that the evolution of genetic variances can drive coevolutionary cycles and yield novel and empirically testable predictions for the sign of linkage disequilibria.

The Models

We begin by describing the assumptions that are common to all three models and then consider several special cases, each of which makes particular assumptions that facilitate mathematical analysis. In all cases we follow coevolutionary dynamics between a single pair of species, either a host and parasite or predator and prey (from this point on we simply refer to the species as host and parasite). We assume that population sizes are sufficiently large for the effects of random genetic drift to be ignored, and we assume that individuals within species mate randomly. Interactions between the two species are assumed to be mediated by a single quantitative trait in each species with the parasite trait denoted as z_p and the host trait denoted z_h. We further assume that individuals encounter one another at random and that the probability of a parasite successfully attacking a host decreases with the squared distance between their phenotypes. Thus, our model is appropriate for those interactions mediated by the degree of phenotypic matching between host and parasite traits (e.g., Abrams and Matsuda 1997; Benkman 1999; Soler et al. 2001). Specifically, we assume that the probability of successful parasite attack is

$$\rho(z_h, z_p) = \mathrm{Exp}[-\alpha(z_h - z_p)^2], \tag{1}$$

where z_h and z_p are the phenotypes of individual host and parasite, respectively, and α measures how rapidly the probability of successful attack declines with phenotypic distance. This probability will play a critical role in determining the fitness of different phenotypes in each of the modeling approaches we consider.

Two Extreme Assumptions: Standing Genetic Variance Fixed or Absent

We begin by considering two cases that have been analyzed previously. Our goal is to level the playing field of comparison by removing any nonessential components of previous models and challenging the two approaches with an identical fitness function—namely the matching phenotypes model described previously. Developing predictions for the fixed genetic variance case is straightforward and follows the previous work of Gavrilets (1997) with only slight modification (Appendix 1, available online only at http://dx.doi.org/10.1554/05-141.1.s1). The key assumptions of this approach are that selection is weak and that additive genetic variance is fixed. With these assumptions, only the mean phenotypes of the two species change:

$$\Delta\bar{z}_h = 2s_hG_h(\bar{z}_h - \bar{z}_p) \quad \text{and} \tag{2a}$$

$$\Delta\bar{z}_p = 2s_pG_p(\bar{z}_h - \bar{z}_p), \tag{2b}$$

where G_i is the additive genetic variance in species i, and s_i is a function of ρ measuring the sensitivity of fitness in species i to the degree of phenotypic matching between species (Appendix 1 available online).

As reported by Gavrilets (1997), there are only two possible outcomes of coevolution in this model. If the host has a more rapid response to selection (i.e., $s_hG_h > s_pG_p$), the host will escape and both host and parasite trait values will become increasingly large (or small) with the host trait increasing (or decreasing) at a greater rate. Alternatively, if the parasite has a more rapid response to selection (i.e., $s_hG_h < s_pG_p$), the parasite will trap the host and the distance between host and parasite mean phenotypes will decrease to zero. As noted by Gavrilets (1997), the possibility that trait values become infinite is biologically unreasonable; for this reason, Gavrilets (1997) suggested that strong stabilizing selection must be present for trait values to remain finite. Although this is clearly true for fixed genetic variances, we will see later that allowing genetic variance to evolve eliminates the need for stabilizing selection.

The second approach that has been profitably applied to the study of predator-prey or host-parasite coevolution is based on the theory of adaptive dynamics (Dieckmann and Law 1996; Metz et al. 1996; Geritz et al. 1998). In this case, a critical genetic assumption necessary for a tractable analysis is that standing genetic variance is absent, and that evolution is instead driven by new mutations that transiently introduce genetic variation. Our adaptive dynamics model of host-parasite interactions follows the previous work of Dieckmann et al. (1995), Marrow et al. (1996), and Doebeli and Dieckmann (2000) with only minor modification. Under the assumptions that ecological host-parasite dynamics are given by Lotka-Volterra equations, mutations occur sufficiently rarely so that resident populations are always in ecological equilibrium, and mutants that can invade will go to fixation, the adaptive dynamics of the traits z_h and z_p are given by (Appendix 2, available online only at http://dx.doi.org/10.1554/05-141.1.s2):

$$\frac{dz_h}{dt} = -\gamma_h \cdot m_h(z_h, z_p) \cdot \frac{\partial \rho}{\partial z_h}(z_h, z_p) \quad \text{and} \tag{3a}$$

$$\frac{dz_p}{dt} = \gamma_p \cdot m_p(z_h, z_p) \cdot \frac{\partial \rho}{\partial z_p}(z_h, z_p). \tag{3b}$$

Here z_h and z_p denote the resident trait values at time t in the host and parasite, respectively, and γ_h and γ_p are ecological quantities affecting the response to selection in the two species (Appendix 2 available online). The quantities $m_h(z_h, z_p)$ and $m_p(z_h, z_p)$ describe the rate and distribution of the mutational process and play a role equivalent to that of standing genetic variance in the dynamical equations for the fixed genetic variance case (compare eqs. 2 and 3). Appendix 2 (available online) explains that just as with the fixed genetic variance case, the only evolutionary equilibrium states of equation (3) are those in which parasite and host have identical phenotypes ($z_h = z_p$). Such a matching equilibrium is locally stable whenever

$$\gamma_h m_h < \gamma_p m_p, \tag{4}$$

where m_h and m_p describe the mutational variance at equilibrium. If this condition does not hold, the matching equilibrium is unstable and the trait values of both species will become increasingly large (or small) with the parasite trait increasing (or decreasing) at a greater rate. Thus, the adaptive dynamics model exhibits dynamics qualitatively identical to the quantitative genetics model (2). Of particular importance is the fact that neither model predicts coevolutionary cycling.

A Genetically Explicit Approach

Both of the approaches presented in the previous section make genetic assumptions that are not likely to be satisfied in all biological systems (e.g., Falconer and Mackay 1996; Begin and Roff 2003). In an effort to fill this gap, we develop and analyze a genetically explicit model that allows the presence of standing genetic variance and allows this genetic variance to evolve. Our general approach will be to apply the multilocus techniques developed by Barton and Turelli (Barton and Turelli 1991; Turelli and Barton 1994) and recently extended by Kirkpatrick et al. (2002) to coevolutionary interactions mediated by quantitative traits.

Developing a genetically explicit model requires that we determine how genotypes are translated into phenotypes. Our specific assumption is that the phenotype of an individual is determined by the additive action of an arbitrary number of diallelic haploid loci with arbitrary phenotypic effects:

$$z_i = \bar{z}_i + \sum_{j=1}^{n_i} b_{i,j}(X_{i,j} - p_{i,j}), \tag{5}$$

where $b_{i,j}$ is the phenotypic effect of locus j on trait z_i in species i, $X_{i,j}$ is an indicator variable that takes value 1 or 0 depending on the allele carried by an individual at locus j, and $p_{i,j}$ is the frequency of the 1 allele in species i at locus j. We also assume that the trait is perfectly heritable; including a random environmental component to phenotype in equation (5) would be straightforward but would have no qualitative impact on the results.

The next step in our development of the genetically explicit model is to determine how an individual's phenotype maps to fitness. Assuming that individuals encounter one another at random, the fitness of an individual with phenotype z_i is equal to:

$$W(z_h) = 1 - \xi_h \sum \rho(z_h, z_p)\phi_p \quad \text{and} \tag{6a}$$

$$W(z_p) = 1 + \xi_p \sum \rho(z_h, z_p)\phi_h, \tag{6b}$$

where ξ_i measures the fitness consequence of a successful parasite attack for species i, $\rho(z_h, z_p)$ is the probability of successful parasite attack in encounters between individuals with phenotypes z_h and z_p determined from equation (1), ϕ_j is the frequency distribution of phenotype z_j in interacting species j, and the sum is taken over all possible phenotypes in the interacting species j.

Equations (5) and (6) provide recipes for translating genotypes into phenotypes, and phenotypes into fitness. To make further progress, however, we must assume that the probability of successful parasite attack depends only weakly upon the phenotypes of the interacting individuals. Mathematically, this allows us to approximate the exponential function in equation (1) with a quadratic, making evaluation of the sum in equation (6a,b) straightforward and demonstrating that the fitnesses of host and parasite are given by:

$$W(z_h) \approx 1 - \xi_h + \alpha\xi_h[(z_h - \bar{z}_p)^2 + V_p] \quad \text{and} \tag{7a}$$

$$W(z_p) \approx 1 + \xi_p - \alpha\xi_p[(\bar{z}_h - z_p)^2 + V_h], \tag{7b}$$

where V_i is the phenotypic variance in species i. Equations (7a,b) demonstrate that the curvature of the host fitness surface is always positive, whereas the curvature of the parasite fitness surface is always negative. We will see that the contrasting curvature of parasite and host fitness surfaces has important consequences for the evolution of genetic variance in each species and ultimately for the outcome of coevolution.

Our final assumption is that selection is weak relative to the rate of recombination. Under these conditions, a steady state will be reached where statistical associations between loci (disequilibria) are small and changing slowly relative to allele frequencies (Barton and Turelli 1991; Nagylaki 1993; Kirkpatrick et al. 2002). With these simplifying assumptions, the changes in allele frequencies over a single generation are given by:

$$\Delta p_{p,j} = \mu_p(1 - 2p_{p,j}) + s_p b_{p,j} p_{p,j} q_{p,j} \times [2(\bar{z}_h - \bar{z}_p) + b_{p,j}(-1 + 2p_{p,j})] \quad \text{and} \tag{8a}$$

$$\Delta p_{h,j} = \mu_h(1 - 2p_{h,j}) + s_h b_{h,j} p_{h,j} q_{h,j} \times [2(\bar{z}_h - \bar{z}_p) - b_{h,j}(-1 + 2p_{h,j})], \tag{8b}$$

where $s_h = \alpha\xi_h/(1 - \xi_h)$ and $s_p = \alpha\xi_p/(1 + \xi_p)$, and μ_i is the rate at which 0 alleles mutate to 1 alleles and vice versa in species i (Appendix 3, available online only at http://dx.doi.org/10.1554/05-141.1.s3). The population mean phenotypes $\bar{z}_h$ and $\bar{z}_p$ that appear in equations (8a,b) are given by:

$$\bar{z}_h = \sum_{j=1}^{n_h} b_{h,j} p_{h,j} \quad \text{and} \tag{9a}$$

$$\bar{z}_p = \sum_{j=1}^{n_p} b_{p,j} p_{p,j}, \tag{9b}$$

with the sums taken over all loci in the host, n_h, and parasite, n_p, respectively (Appendix 3 available online). Equations (8a,b) are valid for any distribution of effects across loci and for any values of recombination, provided that recombination remains sufficiently frequent relative to the strength of selection (Kirkpatrick et al. 2002). Although the statistical associations between loci (disequilibria) do not appear in equations (8a,b), their values are not zero. We will see later, in fact, that our model provides interesting insights into the magnitude and sign of disequilibria in each of the interacting species.

Equations (8a,b) allow us to study the dynamics and outcome of coevolution when both trait means and genetic variances evolve. Because our primary goal is to determine how the evolution of genetic variance changes the outcome and dynamics of coevolution, we focus on the equilibrium characterized by matching host and parasite trait means ($\bar{z}_h = \bar{z}_p$) identified by previous models as the unique coevolutionary equilibrium (Dieckmann et al. 1995; Gavrilets 1997; Doebeli and Dieckmann 2000; Nuismer and Doebeli 2004). Equations (8a,b) show that this equilibrium occurs any time allele frequencies are equal to one-half at all loci ($p_{i,j} = 1/2$) and the sum of allelic effects across loci is equal for the two species. In addition to showing that the matching equilibrium identified by previous models can occur in our multilocus model, equations (8a,b) show that the incorporation of explicit multilocus genetics leads to a myriad of other equilibria as well. We make no effort to elaborate on these additional equilibria. Instead, we confine our analysis to determining the conditions that allow the matching equilibrium characterized by allele frequencies that are equal to one-half across all loci to be stable. Later we will report results from numerical simulations that suggest our focus on this specific equilibrium is justified.

We investigated the conditions that allow this matching equilibrium to be evolutionarily stable by performing a local stability analysis of the system of equations (8a,b) around the matching equilibrium ($p_{i,j} = 1/2$ for all i, j). Without making an additional assumption, however, a general analysis for an arbitrary number of loci is not possible. The key assumption is that the effects of all loci are identical within a species and inversely proportional to the number of loci ($b_{i,j} = 1/n_i$). Scaling the effects of loci in this way, however, does have two important effects. First, it constrains the phenotypes of both species to lie between zero and one. This constraint is actually advantageous, as it levels the playing field for the two species and prevents a host species with more loci from escaping the parasite simply as a consequence of its greater phenotypic range. Second, it causes the maximum possible genetic variance to decrease as the number of loci increases. Thus, with all else being equal, the species with a greater number of loci has a smaller genetic variance. Once the effects of all loci have been scaled in this fashion, it is possible to show that the matching equilibrium will be stable anytime the following pair of eigenvalues is less than zero:

$$\mathrm{E}_1 = \frac{s_p}{n_p^2} - 4\mu_p \quad \text{and} \tag{10a}$$

$$\mathrm{E}_2 = \frac{(n_h - 1)s_h}{4n_h^2} - \frac{(n_p - 1)s_p}{4n_p^2} - \mu_h - \mu_p \pm \frac{1}{4n_h^2 n_p^2}\sqrt{K}, \tag{10b}$$

where K is a complicated combination of terms (Appendix 4, available online only at http://dx.doi.org/10.1554/05-141.1.s4).

The stability conditions (10a,b) reveal that two important conditions must be met for the matching equilibrium to be stable. First, the parasite mutation rate must be greater than the strength of parasite selection divided by four times the squared number of parasite loci. This requirement is reflected in eigenvalue (10a). Biologically, this result arises because the parasite population experiences continuous stabilizing selection that acts to erode genetic variance. In contrast, the host experiences disruptive selection that acts to increase genetic variance. As a consequence, if parasite mutation rates are too low relative to the strength of selection, parasite genetic variance ultimately becomes sufficiently eroded for the host to escape from the matching equilibrium (Fig. 1A,B). For biologically plausible mutation rates and strengths of selection, this condition is likely to be satisfied only when the parasite trait is determined by many loci. The second condition that must be met is revealed by eigenvalue (10b). Numerical investigation of this eigenvalue reveals that the matching equilibrium is more likely to be stable if the per locus strength of parasite selection exceeds the per locus strength of host selection. If this condition does not hold, the host may have a greater rate of evolution than the parasite, allowing it to escape from the matching equilibrium (Fig. 1C,D). This result mirrors the classical result from models in which genetic variance is assumed fixed (Gavrilets 1997). In addition to illuminating novel and more restrictive requirements for the stability of the matching equilibrium, conditions (10a,b) suggest that cyclical dynamics are possible in this system when K is less than zero, a suggestion supported by genetically explicit numerical simulations (Fig. 1). Indeed, numerical evaluation of K shows that it can be less than zero over a broad range of biologically plausible parameter values, indicating that the evolution of genetic variance greatly increases the likelihood of cyclical coevolutionary dynamics (Appendix 4 available online).

Although the analytical results presented above are quite insightful, they tell us little about the global dynamics of the system. To investigate these dynamics further and to verify the accuracy of conditions (10a,b), we conducted deterministic numerical simulations. These simulations followed the frequency of all haploid genotypes directly but were in all other respects identical to the analytical model. We performed two separate sets of simulations. In the first, initial genotype frequencies were set to values that assumed all allele frequencies were equal to one-half and that linkage disequilibrium was initially absent. These genotype frequencies were then randomly perturbed ($\pm 0.01\%$). Simulations were run for a variety of parameter values that either did or did not satisfy stability conditions (10a,b). Only if selection was very strong and/or recombination weak relative to selection did the local stability conditions break down. Even in those cases where conditions (10a,b) break down, their qualitative predictions remain intact (e.g., stability continues to require a threshold rate of mutation in the parasite). These numerical results provide strong support for the accuracy of the local stability conditions (10a,b). In the second set of simulations, we investigated whether the local stability con-

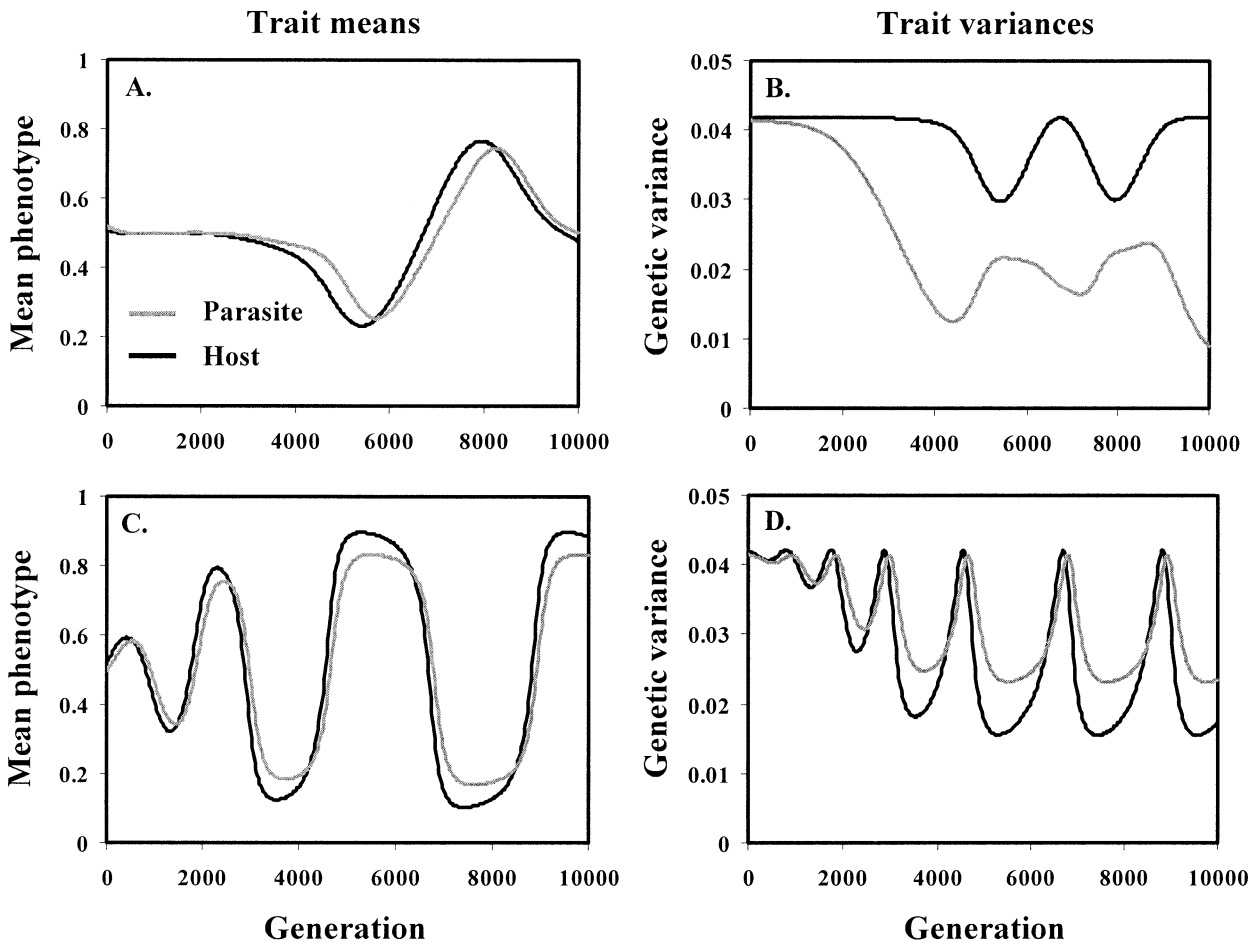

FIG. 1. Coevolutionary dynamics of trait means (left) and trait variances (right) when one of the two stability conditions given by conditions (10a,b) is not satisfied. In panels A and B, condition (10a) is not satisfied. As a result, parasite genetic variation is slowly eroded. Past some critical threshold, around generation 3000 in the figure, parasite genetic variation becomes so depleted that it can no longer prevent the host population from escaping. In panels C and D, condition (10b) is not satisfied. As a result, selection acting on the host population is sufficiently strong relative to the strength of selection acting on the parasite that the host can immediately begin to escape. Ultimately, both cases lead to cyclical dynamics not possible in models where genetic variance does not evolve. Coevolutionary trajectories come from explicit multilocus numerical simulations. Parameter values for panels A and B: $n_h = n_p = 6$, $b_h = b_p = 1/n_h$, $s_h = 0.05$, $s_p = 0.10$, $\mu_h = 0.00001$, $\mu_p = 0.0001$, $r_h = r_p = 0.5$. Parameter values for panels C and D: $n_h = n_p = 6$, $b_h = b_p = 1/n_h$, $s_h = 0.15$, $s_p = 0.10$, $\mu_h = 0.00001$, $\mu_p = 0.0008$, $r_h = r_p = 0.5$. Simulations were initiated with all allele frequencies set to 1/2 then perturbed at random and independently by $\pm$ 0.1.

ditions (10a,b) predicted the global dynamics of the model. In these simulations initial genotype frequencies were drawn at random from a uniform distribution. These simulations demonstrated that, for the majority of parameter combinations we tried, if the local stability conditions (10a,b) are satisfied and selection is sufficiently weak relative to recombination, the system evolves to the matching equilibrium. If the stability conditions (10a,b) are not satisfied, however, multiple coevolutionary outcomes can occur, ranging from persistent cycles to alternative equilibria that represent a balance between directional selection and mutation.

To this point we have focused entirely on the dynamics of allele frequencies and trait means. Our quasi-linkage equilibrium (QLE) analysis also provides interesting insights into the nature of genetic disequilibria between loci. Specifically, our results show that the QLE values of disequilibria in host and parasite are:

$$\tilde{D}_{h,i,j} \approx \frac{s_h b_{h,i} b_{h,j}(1 - r_{h,i,j}) p_{h,i} q_{h,i} p_{h,j} q_{h,j}}{r_{h,i,j}} \quad \text{and} \qquad (11a)$$

$$\tilde{D}_{p,i,j} \approx -\frac{s_p b_{p,i} b_{p,j}(1 - r_{p,i,j}) p_{p,i} q_{p,i} p_{p,j} q_{p,j}}{r_{p,i,j}}, \qquad (11b)$$

where $r_{i,j,k}$ is the recombination rate between loci j and k in species i. Equations (11a,b) reveal a simple yet important conclusion: linkage disequilibria should be negative in the parasite but positive in the host anytime coevolution is mediated by phenotypic matching. This result arises because selection for matching in the parasite preferentially eliminates individuals with extreme phenotypes. In the host, however, selection favors individuals that do not match the parasite, which consistently favors individuals with more extreme phenotypes. Thus, in natural populations of hosts and parasites where the evolution of two target quantitative traits

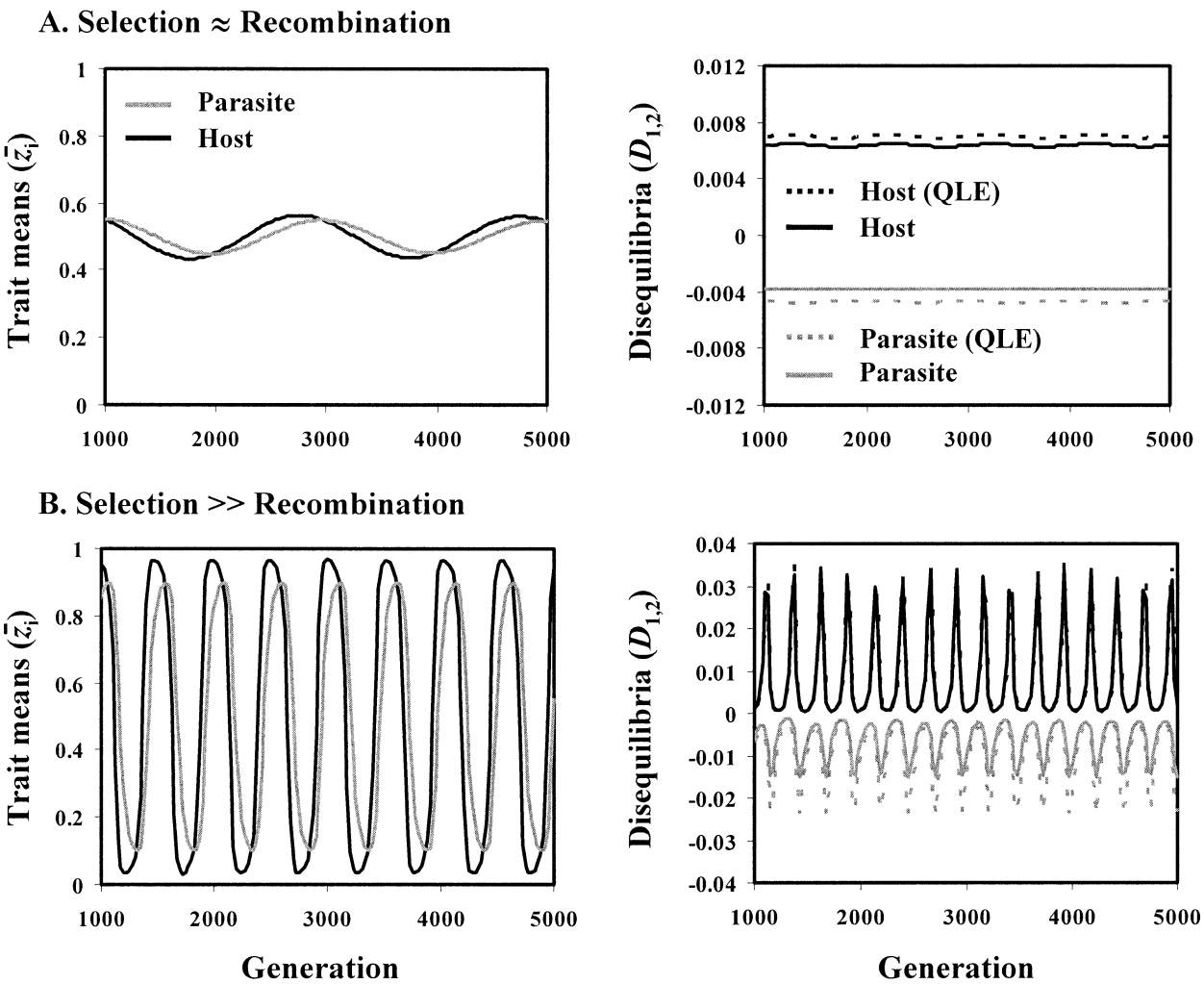

FIG. 2. Coevolutionary dynamics of trait means (left) and pairwise disequilibria (right) for a case where selection is equivalent to the recombination rate (A) and a case where selection is significantly stronger than the recombination rate (B). The right panels show the quasi-linkage equilibrium (QLE) predictions for $D_{1,2}$ in host and parasite as well as the actual value of $D_{1,2}$ observed in deterministic simulations. Although only $D_{1,2}$ is shown for the sake of clarity, qualitatively similar patterns are observed for any of the pairwise disequilibria $D_{i,j}$. Parameter values were: $n_h = n_p = 5$, $b_h = b_p = 1/n_h$, $s_h = 0.075$, $s_p = 0.05$, $\mu_h = 0.0005$, $\mu_p = 0.0005$, $r_h = r_p = 0.05$ for panel A; and $n_h = n_p = 5$, $b_h = b_p = 1/n_h$, $s_h = 0.375$, $s_p = 0.25$, $\mu_h = 0.0005$, $\mu_p = 0.0005$, $r_h = r_p = 0.05$ for panel B. Even though panel B grossly violates the QLE assumptions, the QLE predictions remain qualitatively correct for the sign of $D_{1,2}$. Simulations were initiated with all allele frequencies set to 0.45 then perturbed at random and independently by ± 0.1.

is driven primarily by coevolutionary matching, loci contributing to the host trait should exhibit positive disequilibria, whereas loci contributing to the parasite trait should exhibit negative disequilibria. This result is very robust, with numerical simulations demonstrating that equations (11a,b) accurately predicts the sign of host and parasite linkage disequilibria across virtually all parameter values, including those that grossly violate QLE assumptions (Fig. 2).

DISCUSSION

Our results demonstrate that the evolution of genetic variance can have important consequences for the coevolutionary dynamics of interacting species. This can be most clearly seen by comparing results from our explicit multilocus model with results from previous models that assume standing genetic variance is fixed or absent. If genetic variance is assumed to be fixed or absent and the action of stabilizing selection is ignored, coevolution leads to one of only two possible outcomes. If the parasite has a greater response to selection, host and parasite evolve to a stable matching equilibrium where the population mean phenotypes of the two species are equal. If, in contrast, the host has a greater response to selection, population mean phenotypes of the two species increase or decrease in perpetuity with the parasite mean phenotype falling steadily behind (e.g., Gavrilets 1997). Analysis of our multilocus model reveals that this dichotomy is an oversimplification. For instance, our results demonstrate that only specific combinations of selection, mutation, and numbers of loci allow matching population mean phenotypes of host and parasite to be stable. More importantly, our results demonstrate that when the matching equilibrium is unstable, host and parasite population mean phenotypes can cycle rath-

er than increasing or decreasing indefinitely, as is frequently observed in single locus models of coevolutionary interactions (e.g., Jayakar 1970; Seger 1988; Gavrilets and Hastings 1998; Nuismer et al. 2003).

It is worth considering in detail why the multilocus model makes such strikingly different predictions for the dynamics and outcome of coevolutionary interactions between hosts and parasites. Consider, for instance, the case of the matching equilibrium in which population mean phenotypes of host and parasite are equal. In the fixed genetic variance and adaptive dynamics models, this equilibrium is stable if the parasite response to selection exceeds that of the host. Our multilocus model, however, predicts that this equilibrium is stable only for certain combinations of mutation rates, selection strengths, and numbers of genetic loci. This discrepancy can be readily understood by considering how the evolution of genetic variance, which is only possible in the multilocus model, alters the relative rates of evolution in the two species when they are slightly perturbed from the matching equilibrium. Specifically, the response to selection in the parasite decreases as stabilizing selection generated by selection for matching the host gradually erodes parasite additive genetic variance (see eq. 7). In contrast, the response to selection in the host is unchanged or slightly increased by disruptive selection, which inflates host genetic variance (see eq. 7). Unless the rate of mutation in the parasite is sufficient to keep additive genetic variance above some critical threshold, the response to selection of the parasite will drop below that of the host and the host population mean will evolve away from that of the parasite. This phenomenon was previously described by Nuismer and Doebeli (2004) based upon results of numerical simulations.

The second major difference between our multilocus model and previous approaches is the prediction of coevolutionary cycles even in the absence of stabilizing selection. Once again, it appears that the evolution of genetic variance is responsible. This can be clearly seen by considering a case in which the matching equilibrium is predicted to be locally unstable and oscillatory (Fig. 3). In this case, we expect the host population mean phenotype to initially begin to decrease (alternatively it could increase), with the parasite population subsequently tracking behind (Fig. 3A,B). This initial phase of decreasing phenotypic values is driven by selection that favors individual hosts with phenotypes less than the parasite population mean. As the mean phenotype of the host population continues to decrease, however, host genetic variance decreases as the population is pushed up against the impassible boundary of the trait interval. As a consequence, the rate of evolution in the host slows (Fig. 3A), and its trait distribution becomes skewed. At the same time, however, the parasite population mean continues to decrease at a rapid rate, because it lags behind the host and hence is less affected by the approaching trait interval boundary and its associated loss of genetic variance. Over time the parasite distribution becomes increasingly similar to that of the host population (Fig. 3C). Past some critical point, the host and parasite distributions become sufficiently overlapping and skewed for the direction of selection acting on the host population to reverse; as a result the host mean phenotype begins to increase. Once the host mean has increased sufficiently, the pattern of selection acting on the parasite also shifts, and the parasite population begins to evolve an increased mean phenotype as well (Figs. 3A,D). The ultimate result is that both host and parasite trait means and variances cycle over evolutionary time, with the frequency of cycles largely determined by the number of loci and strength of selection in each of the interacting species.

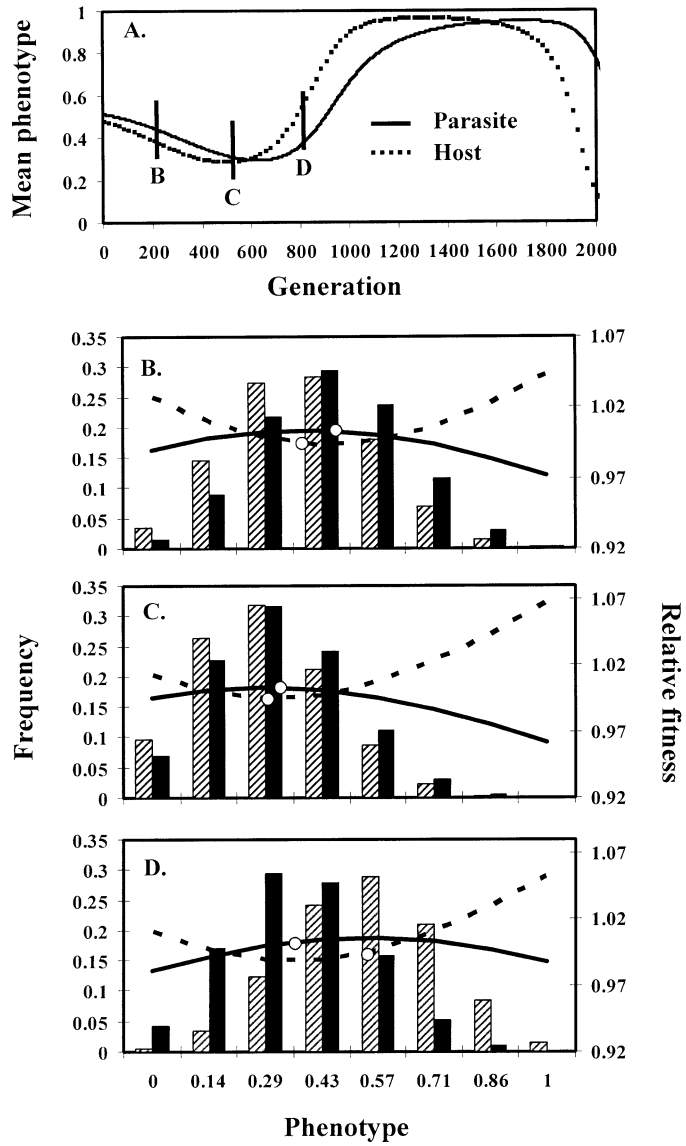

FIG. 3. Coevolutionary dynamics of trait means (A) and phenotypic distributions (B–D). Panel A shows trait means in host and parasite across 2000 generations for a case where cyclical dynamics are predicted by conditions (10a,b). The vertical lines indicate the points in time for which trait distributions are shown in panels B–D. Panels B–D show the frequency distribution of host (dashed bars) and parasite (solid bars) as well as the fitness of host (dashed line) and parasite phenotypes (solid line) for generations 200, 500, and 800. White circles represent the population mean of host and parasite. Parameter values were: $n_h = n_p = 7$, $b_h = b_p = 1/n_h$, $s_h = 0.2$, $s_p = 0.1043$, $\mu_h = 0.00001$, $\mu_p = 0.00001$, $r_h = r_p = 0.5$. Simulations were initiated with all allele frequencies set to 1/2 then perturbed at random and independently by ± 0.1.

The mechanism underlying the cyclic dynamics we de-

scribe here is, at least in some cases, quite distinct from the mechanism responsible for cyclic dynamics in single-locus models (e.g., Seger 1988; Gavrilets and Hastings 1998). This is clearly true for cycles that emerge when the matching equilibrium is destabilized by the erosion of genetic variance in the parasite (e.g., Fig. 1A). In the haploid single-locus models studied previously, the genetic variance is simply a function of the mean phenotype and hence cannot change while the means are fixed. Thus, the mechanism generating the cycles described above, which is based on the loss of genetic variance in the parasite when both species means are at a matching equilibrium, cannot operate in these single-locus models.

Our multilocus model makes assumptions that are quite different from those of the adaptive dynamics and fixed genetic variance models (eqs. 2 and 3). For this reason, it is not surprising that the results from the multilocus model differ substantially from those of the other two approaches. What is surprising, however, is that the predictions of the fixed genetic variance and adaptive dynamics models are identical. Our comparison here reveals that, despite their substantially different assumptions, the two modeling frameworks share two critical features. First, both assume an infinite trait interval, and thus implicitly or explicitly assume that, sooner or later, new mutations arise that are capable of producing any phenotypic value. Second, both approaches assume that selection does not directly affect genetic variation. In the case of the fixed genetic variance approach, this is obviously incorporated in the assumption that genetic variance is constant. In the adaptive dynamics approach, however, this feature is more subtle because the rate at which genetic variation is introduced to the population through mutation, $m_h(z_h, z_p)$ and $m_p(z_h, z_p)$ in equation (3), can actually change over time in response to changes in population density. What remains true, however, is that the rate at which new genetic variation is generated does not change in direct response to selection, only as an indirect response to changes in population density. Our results show that it is this direct response of genetic variation to selection, lacking in both the fixed genetic variance and adaptive dynamics approaches, that commonly destabilizes the matching equilibrium (Fig. 1A,B).

In addition to illuminating the importance of genetic variance for coevolving interactions, our multilocus model has revealed a novel prediction for the sign of linkage disequilibria in the interacting species. Specifically, our results predict that host linkage disequilibria should be positive, whereas parasite linkage disequilibria should be negative. This result arises because coevolution based on phenotypic matching generates a host fitness surface with positive curvature (of disruptive form; Fig. 3) but a parasite fitness surface with negative curvature (of stabilizing form; Fig. 3). Both the predicted sign of linkage disequilibria and predicted curvature of the fitness surface are very robust (Fig. 2) and present unique opportunities for detecting the signature of coevolutionary selection acting on quantitative traits if functionally important loci for these traits are known. Although observed patterns of linkage disequilibria could be due to other evolutionary forces such as gene flow or genetic drift (Li and Nei 1974; Mallet et al. 1990; Lenormand and Otto 2000), the likelihood of these other forces consistently leading to positive linkage disequilibria in hosts but negative linkage disequilibria in parasites seems very small. The same logic applies to predictions based upon a comparison of fitness surfaces. For this reason, tests based upon a comparison of host and parasite linkage disequilibria or phenotypic selection (e.g., Berenbaum et al. 1986; Berenbaum and Zangerl 1992; Benkman 1999; Clayton et al. 1999; Benkman et al. 2001) are more likely to correctly identify geographic regions of coevolutionary selection than those based upon comparison of trait means (Brodie et al. 2002; Zangerl and Berenbaum 2003). Accurately identifying regions where coevolutionary selection is operating is critical to evaluating the importance of these coevolutionary hot spots for the overall dynamics of geographically structured coevolution (Thompson 1997, 2005; Gomulkiewicz et al. 2000; Brodie et al. 2002). In addition, identifying regimes of disruptive selection due to coevolutionary interactions can be important for studying processes of adaptive diversification and sympatric speciation (Doebeli and Dieckmann 2000; Day and Young 2004; Dieckmann et al. 2004).

At this point, it is worth considering several potentially important limitations of our modeling approach. First and foremost, it is important to emphasize that we have considered only one possible form of coevolutionary selection. Specifically, we have assumed that coevolutionary selection is based upon the degree of phenotypic matching between host and parasite phenotypes (e.g., Clayton et al. 1999; Soler et al. 2001, 2003). This assumption precludes the direct application of our results to other forms of coevolutionary selection, such as escalation, that have been demonstrated to be important in several well-studied natural systems (e.g., Berenbaum et al. 1986; Brodie and Brodie 1999; Bergelson et al. 2001). Second, we have focused on a very simple form of haploid genetic architecture where all loci have equal and additive phenotypic effects. Thus, our results largely ignore the potentially important effects of dominance and unequal phenotypic effects across loci. Finally, we have ignored extrinsic stabilizing selection, which has been shown to be important in shaping coevolutionary dynamics in other models (e.g., Gavrilets 1997; Doebeli and Dieckmann 2000; Nuismer and Kirkpatrick 2003). A potentially important consequence of ignoring stabilizing selection is that our prediction of positive host linkage disequilibrium could be incorrect in some cases. This would only occur, however, if the strength of extrinsic stabilizing selection exceeded the strength of coevolutionary selection. Addressing the relative importance of these issues offers interesting avenues of exploration for future work.

We have used a comparison of three modeling approaches to illustrate how the evolution and coevolution of standing genetic variance can radically alter the dynamics and outcomes of coevolving species interactions. Our results also form an important bridge between models of quantitative trait coevolution that incorporate genetics implicitly (e.g., Gavrilets 1997; Doebeli and Dieckmann 2000; Nuismer and Kirkpatrick 2003) and those that incorporate explicit genetics but consider only one or two loci (e.g., Seger 1988; Gavrilets and Hastings 1998; Nuismer et al. 1999). Critically evaluating the applicability of each of these approaches to natural

systems will require empirical estimates for the evolutionary stability of genetic variances for traits mediating interspecific interactions. Also important will be the development of coevolutionary models that allow the evolution of additive genetic variance in the absence of a fixed trait interval (e.g., Polechova and Barton 2005). Together with results presented here, these future empirical and theoretical studies should provide a synthetic and comprehensive theory for the coevolutionary dynamics of coevolving quantitative traits.

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