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Evolution

Gene–culture coevolution: Toward a general theory of vertical transmission

(cultural transmission/phenogenotypes/gene–culture disequilibrium/invasion criteria/generalized epistasis)

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ABSTRACT **A general formulation of cultural and genetic transmission is developed. The cultural transmission is vertical and the genetics may involve multiple loci. Each individual is represented by a phenogenotype, and conditions are given under which the evolutionary dynamics of phenogenotype frequencies are reducible to phenogametic or phenoallelic frequencies. The interaction between genes and culture is specified by an association measure, and results on the order of magnitude of this association at equilibrium are presented.**

The development and expression of many traits in humans and other animals are subject to non-genetic influences, some of which may be culturally transmitted (1, 2). The classical theory of such traits partitions the variability among phenotypes into genetic and environmental components (3, 4). This approach is primarily statistical and has had a major impact on animal and plant breeding for agricultural purposes. In some applications to human behavioral genetics, the linear statistical model that underlies this theory has been extended to include vertical cultural transmission from parents to offspring (5–9).

Recent progress in the general evolutionary theory of continuously varying traits under stabilizing selection has incorporated advances in assumptions about the underlying genetic model (10–12) and has revealed new properties of the structure of variation in quantitative traits (13). With few exceptions (ref. 14), however, these treatments have not included both natural selection and cultural transmission.

Feldman and Cavalli-Sforza (15) introduced an evolutionary theory of culturally transmitted dichotomous traits whose transmission depends on parental phenotypes and/or genotypes, and which are subject to natural selection. Those authors established that the interaction between genetic and cultural processes in such models can result in important departures from the evolutionary trajectories expected from classical population-genetics theory. Among the more interesting findings of this analysis is that heterozygote advantage in the cultural transmission of an advantageous phenotype is not sufficient to guarantee the existence of a stable genetic polymorphism. Further, in comparison to simple models of differential viability among genotypes, the rate of evolution under mixed transmission can be severely retarded (see also ref. 16).

Models that include genotype-dependent cultural transmission have been used to study the evolution of communication and language (17–19), altruism (20), and other learned traits (21), as well as to address the apparent correlation between the cultural custom of dairying and milk use and the genetic trait of lactose absorption (refs. 22 and 23; see also ref. 24).

In most of these treatments, simplifying assumptions were made about the rules of transmission or the action of natural selection. For example, much of the analysis in ref. 15 assumed uniparental cultural transmission—i.e., that only one parent's phenotype was important in determining that of the offspring. Also in this previous work, selection acting on offspring was independent of their parents' genotypes and phenotypes. The first objective of the present paper is to remove such restrictions and to develop a general formulation for the evolution of traits whose transmission depends on the phenotypes and genotypes of both parents without constraints on the number of genotypes or phenotypes. To accomplish this we use and extend the notion of family triplets introduced by Feldman and Aoki (25) in their study of the evolution of sign language in the presence of hereditary deafness. From these triplets the dynamics of phenotypes, gametes, and alleles may be inferred as well as conditions for protected genetic and phenotypic polymorphisms. We also generalize the idea of gene–culture disequilibrium (26) and attempt to relate the selection regime and the transmission rule to interactions between the frequencies of genotypes and phenotypes.

Model of Transmission and Selection

The population is assumed to be large enough that sampling effects may be ignored. Each individual is specified by its phenotype and its genotype. The possible genotypes are denoted by G_i ($i = 1, 2, \ldots, L$); at this stage it is not necessary to specify the number of alleles or loci. The possible phenotypes are F_α ($\alpha = 1, 2, \ldots, M$). An individual of genotype i and phenotype α is said to have the *phenogenotype* $FG_{\alpha i}$. The passage between generations of genetic and cultural information is described by a *familial transmission matrix* whose entries $T^{ijk}_{\alpha\beta\gamma}$ stand for the probability that a mother and father of phenogenotypes $FG_{\alpha i}$ and $FG_{\beta j}$, respectively, produce an offspring of phenogenotype $FG_{\gamma k}$.

Genetic transmission is described by the usual matrix $\mathbf{T}_g$ of probabilities $T_g\{ij \rightarrow k\}$ that a mother and father of genotypes G_i and G_j, respectively, produce a child of genotype G_k. Thus $T_g\{ij \rightarrow k\} = \Sigma_{\alpha\beta\gamma} T^{ijk}_{\alpha\beta\gamma}$. As examples, if the genotype is determined by one locus with alleles A and a then, in the absence of mutation, $T_g\{AA, Aa \rightarrow AA\} = 1/2$, etc. If allele A mutates to a at rate μ then, ignoring terms $0(\mu^2)$, $T_g\{AA, Aa \rightarrow AA\} = (1 - 2\mu)/2$ and $T_g\{AA, aa \rightarrow aa\} = \mu$. For two loci with alleles A and a at the first and B and b at the second, and recombination fraction R, then $T_g\{aB/ab, Ab/aB \rightarrow ab/ab\} = R/4$, etc.

Within the genotypic configuration of each family, phenotypic transmission is described by the matrix $\mathbf{T}_{ijk}$ whose entries $T_{ijk}\{\alpha\beta \rightarrow \gamma\}$ are the probabilities that a mother and father of phenotypes F_α and F_β, respectively, produce an offspring of phenotype F_γ, conditional upon their respective genotypes being i, j and k ($i, j, k = 1, 2, \ldots, L$). Clearly $\Sigma_k T_g\{ij \rightarrow k\} = 1$ and $\Sigma_\gamma T_{ijk}\{\alpha\beta \rightarrow \gamma\} = 1$. Analysis under

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completely general transmission is intractable, so we assume that the values of the phenotypes in the family do not affect the rules of genetic transmission so that

$$T^{ijk}_{\alpha\beta\gamma} = T_g\{ij \to k\}T_{ijk}\{\alpha\beta \to \gamma\}. \quad [1]$$

Most of the cultural transmission schemes studied previously (15, 17–21, 25, 26) are special cases of Eq. 1. In a family with parents $FG_{\alpha i}$ and $FG_{\beta j}$ the viability of an offspring $FG_{\gamma k}$ is denoted by $w^{\alpha\beta\gamma}_{ijk}$. The frequency of the phenogenotype $FG_{\alpha i}$ is denoted by $P_\alpha(i)$ so that the frequency of phenotype F_α is $\Sigma_i P_\alpha(i)$, which we denote as P_α, while the frequency of genotype G_i is $\Sigma_\alpha P_\alpha(i)$, which we denote as $P(i)$. Then, under the assumption of random mating, the dynamical system connecting the frequencies of phenogenotypes in the next generation, denoted by the prime, with those in the present takes the form

$$\bar{w}P'_\gamma(k) = \sum_{ij}\sum_{\alpha\beta} w^{\alpha\beta\gamma}_{ijk}T_g\{ij \to k\}T_{ijk}\{\alpha\beta \to \gamma\}P_\alpha(i)P_\beta(j), \quad [2]$$

where

$$\bar{w} = \sum_{ijk}\sum_{\alpha\beta\gamma} w^{\alpha\beta\gamma}_{ijk}T_g\{ij \to k\}T_{ijk}\{\alpha\beta \to \gamma\}P_\alpha(i)P_\beta(j)$$

is the mean fitness in the population. In Eq. 2, $w^{\alpha\beta\gamma}_{ijk}$ may be viewed as including fertility components of selection, while $T_g\{\ \}$ may allow for segregation distortion.

It is not a significant restriction to assume that $T_g\{ij \to k\} = T_g\{ji \to k\}$, although such symmetry may not be the general case for the viabilities or the phenotypic transmission rule. Nevertheless, if we set

$$\tilde{w}^{\alpha\beta\gamma}_{ijk} = [w^{\alpha\beta\gamma}_{ijk}T_{ijk}\{\alpha\beta \to \gamma\} + w^{\beta\alpha\gamma}_{jik}T_{jik}\{\beta\alpha \to \gamma\}]/2,$$

then Eq. 2 may be written

$$\bar{w}P'_\gamma(k) = \sum_{ij}\sum_{\alpha\beta} \tilde{w}^{\alpha\beta\gamma}_{ijk}T_g\{ij \to k\}P_\alpha(i)P_\beta(j), \quad [2*]$$

where now $\tilde{w}^{\alpha\beta\gamma}_{ijk} = \tilde{w}^{\beta\alpha\gamma}_{jik}$.

If the fitnesses of the phenogenotypes depend only on their genotypes, we call it *genotypic selection*, whereas if they depend only on their phenotypes, it is called *phenotypic selection*. The former entails that $w^{\alpha\beta\gamma}_{ijk} = w_{ijk}$ and the latter $w^{\alpha\beta\gamma}_{ijk} = w^{\alpha\beta\gamma}$ for all sets of indices. Transmission is termed *genotype-independent* if $T_{ijk}\{\alpha\beta \to \gamma\} = T\{\alpha\beta \to \gamma\}$ for *all* genotypes i, j, k. Otherwise transmission is *genotype-dependent*.

Protected Polymorphisms

Case 1. Genotypic selection: $w^{\alpha\beta\gamma}_{ijk} = w_{ijk}$. Sum recursions 2 over γ to obtain

$$\bar{w}P'(k) = \sum_{ij} w_{ijk}T_g\{ij \to k\}P(i)P(j), \quad [3]$$

where $\bar{w} = \Sigma_{ijk}w_{ijk}T_g\{ij \to k\}P(i)P(j)$. Eq. 3 in the genotype frequencies does not depend on the phenotype frequencies. Now sum Eq. 2 over k to obtain

$$\bar{w}P'_\gamma = \sum_{ijk}\sum_{\alpha\beta} w_{ijk}T_{ijk}\{\alpha\beta \to \gamma\}T_g\{ij \to k\}P_\alpha(i)P_\beta(j), \quad [4]$$

where $\bar{w} = \Sigma_{ijk}\Sigma_{\alpha\beta}w_{ijk}T_g\{ij \to k\}P_\alpha(i)P_\beta(j)$. Thus, under genotypic selection the dynamics of phenotype frequencies may be affected by the genotypes, and this is true even if the transmission matrix is genotype-independent and the fitness of an offspring depends only on its own genotype; i.e., $w_{ijk} = w_k$.

Consider a single diallelic locus with genotypes AA, Aa, and aa labeled 1, 2, and 3, respectively. In the neighborhood of $P(3) = 1 - \varepsilon$ it is clear that $P(1)$ is of quadratic order in ε. It is straightforward to derive the condition that allele A increases when it is rare—namely, the condition for *protection* of A from loss. Then we have the following.

Result 1. Alleles A and α are protected from loss if

$$w_{333} < (w_{232} + w_{322})/2 \quad [5a]$$

and

$$w_{111} < (w_{212} + w_{122})/2, \quad [5b]$$

respectively. When both inequalities hold, there is a *protected polymorphism*.

Case 2. Phenotypic selection: $w^{\alpha\beta\gamma}_{ijk} = w^{\alpha\beta\gamma}$. We consider here the case of genotype-independent transmission. Sum the recursions 2 over k. Then

$$\bar{w}P'_\gamma = \sum_{\alpha\beta} \tilde{w}^{\alpha\beta\gamma}P_\alpha P_\beta, \quad [6]$$

where $\bar{w} = \Sigma_{\alpha\beta\gamma}\tilde{w}^{\alpha\beta\gamma}P_\alpha P_\beta$. Now sum Eq. 2 over γ to obtain

$$\bar{w}P'(k) = \sum_{ij}\sum_{\alpha\beta\gamma} \tilde{w}^{\alpha\beta\gamma}T_g\{ij \to k\}P_\alpha(i)P_\beta(j), \quad [7]$$

where $\bar{w} = \Sigma_{ij}\Sigma_{\alpha\beta\gamma}\tilde{w}^{\alpha\beta\gamma}P_\alpha(i)P_\beta(j)$. Thus, under phenotypic selection with genotype-independent transmission, the phenotype frequencies do not depend on the genotypes, but genotype frequencies depend on those of the phenotypes.

Now suppose there are two phenotypes in the population, F_1 and F_2. From Eq. 6 it is clear that F_1 cannot be lost if $\tilde{w}^{221} > 0$ and F_2 cannot be lost if $\tilde{w}^{112} > 0$. Then from Eq. 6 we obtain the following.

Result 2. If $\tilde{w}^{221} = 0$, then F_1 is protected from loss if

$$w^{222} < \tilde{w}^{121}. \quad [8a]$$

If $\tilde{w}^{112} = 0$, then F_2 is protected from loss if

$$\tilde{w}^{111} < \tilde{w}^{122}. \quad [8b]$$

If both **8a** and **8b** hold, there is a protected polymorphism.

Remark. If the generalized fitnesses $\tilde{w}^{\alpha\beta\gamma}$ depend only on the child's phenotype—i.e., $\tilde{w}^{\alpha\beta\gamma} = \tilde{w}^{\gamma}$—then only one of Eqs. **8a** and **8b** can be valid.

Reduction to gamete and allele frequencies. Suppose that the generalized fitnesses do not depend on the parental genotypes; i.e., $\tilde{w}^{\alpha\beta\gamma}_{ijk} = \tilde{w}^{\alpha\beta\gamma}_{k}$. Genotype G_i may be represented as its pair of constituent gametes: $G_i = (g_r/g_s)$ so that $\{(r, s)\}$ is a two-dimensional expansion of the genotype set $\{i\}$. Now define $\Gamma\{rs \to t\}$ as the probability that the genotype $G_i = (g_r/g_s)$ produces the gamete g_t, and let $p_\alpha(t)$ be the probability that an individual has phenotype F_α and produces a gamete g_t. We refer to $p_\alpha(t)$ as *phenogamete* frequencies, where $p_\alpha = \Sigma_t p_\alpha(t)$ is the frequency of F_α and $p(t) = \Sigma_\alpha p_\alpha(t)$ is the frequency of gamete g_t. It is then possible to show the following.

Result 3. The recursions **2*** in phenogenotype frequencies may be reduced to the system

$$\bar{w}p'_\gamma(t) = \sum_{rs}\sum_{\alpha\beta} \tilde{w}^{\alpha\beta\gamma}_{rs}\Gamma\{rs \to t\}p_\alpha(r)p_\beta(s), \quad [9]$$

where $\bar{w} = \Sigma_{rs}\Sigma_{\alpha\beta\gamma}\tilde{w}^{\alpha\beta\gamma}_{rs}p_\alpha(r)p_\beta(s)$ and

$$\tilde{w}^{\alpha\beta\gamma}_{rs} = [w^{\alpha\beta\gamma}_{rs}T_{rs}\{\alpha\beta \to \gamma\} + w^{\beta\alpha\gamma}_{rs}T_{rs}\{\beta\alpha \to \gamma\}]/2, \quad [9a]$$

with $\tilde{w}^{\alpha\beta\gamma}_{rs} = \tilde{w}^{\beta\alpha\gamma}_{rs}$. Here $T_{rs}\{\alpha\beta \to \gamma\}$ is the probability that an individual whose genotype is (g_r/g_s), and whose mother and father are of phenotypes F_α and F_β, respectively, is of phenotype F_γ. The fitness of these individuals is $w^{\alpha\beta\gamma}_{rs}$.

Remark 1. The recursion system **2*** involves phenogenotype frequencies among diploid individuals after selection, whereas system **9** concerns phenogamete frequencies in the gamete pool produced by these individuals.

Remark 2. Recursion system **9** may be summed over γ to produce the well-known recursions in gamete frequencies from multilocus population-genetics theory:

$$\bar{w}p'(t) = \sum_{rs} w_{rs}\Gamma\{rs \to t\}p(r)p(s), \qquad [9b]$$

provided that the selection is genotypic and fitnesses do not depend on parental genotypes.

Special case of one locus. Suppose that the genotypes G_i are defined at a single locus with alleles $\{A_r\}$; i.e., $G_i = A_rA_s$, say. Then in system **9**, $\Gamma\{rs \to t\} = 1/2$ if $r \neq s$ and t coincides with r or s; $\Gamma\{rs \to t\} = 1$ if $r = s = t$; otherwise $\Gamma\{rs \to t\} = 0$. Now $p_\alpha(s)$ is the probability that an individual has phenotype F_α and produces a gamete with allele A_s; in this case we refer to $p_\alpha(s)$ as phenoallele frequencies. From Eq. **9** we then deduce

$$\bar{w}p'_\gamma(t) = \sum_s \sum_{\alpha\beta} \tilde{w}_{st}^{\alpha\beta\gamma} p_\alpha(s)p_\beta(t), \qquad [10]$$

where $\bar{w} = \Sigma_{st}\Sigma_{\alpha\beta\gamma}\tilde{w}_{st}^{\alpha\beta\gamma}p_\alpha(s)p_\beta(t)$. Clearly Eq. **10** generalizes the well-known one-locus frequency recursion in the purely genetic context:

$$\bar{w}p'(t) = \sum_s w_{st}p(s)p(t), \qquad [10a]$$

where $p(s)$ is the frequency of A_s and w_{st} is the viability of A_sA_t.

Protection of alleles from loss. Consider two alleles, A and a, at a single locus. Let $\hat{p}_\alpha^{aa}$ and $\hat{p}_\alpha^{AA}$ be stable isolated equilibria in the boundaries where A and a, respectively, are absent. That is, they solve

$$\bar{w}_{aa}p_\gamma = \sum_{\alpha\beta} \tilde{w}_{aa}^{\alpha\beta\gamma}p_\alpha p_\beta; \qquad \bar{w}_{aa} = \sum_{\alpha\beta\gamma} \tilde{w}_{aa}^{\alpha\beta\gamma}p_\alpha p_\beta, \quad [11a]$$

and

$$\bar{w}_{AA}p_\gamma = \sum_{\alpha\beta} \tilde{w}_{AA}^{\alpha\beta\gamma}p_\alpha p_\beta; \qquad \bar{w}_{AA} = \sum_{\alpha\beta\gamma} \tilde{w}_{AA}^{\alpha\beta\gamma}p_\alpha p_\beta, \quad [11b]$$

respectively. Now introduce two $m \times m$ matrices, $\mathbf{V}_{Aa}^{aa} = \|v_{Aa,aa}^{\beta\gamma}\|$ and $\mathbf{V}_{Aa}^{AA} = \|v_{Aa,AA}^{\beta\gamma}\|$, where

$$v_{Aa,aa}^{\beta\gamma} = \sum_\alpha \tilde{w}_{Aa}^{\alpha\beta\gamma}\hat{p}_\alpha^{aa}, \; v_{Aa,AA}^{\beta\gamma} = \sum_\alpha \tilde{w}_{Aa}^{\alpha\beta\gamma}\hat{p}_\alpha^{AA}. \qquad [12]$$

Then we have the following (see also ref. 27).

Result 4. Let ρ_{Aa}^{aa} and ρ_{Aa}^{AA} be the spectral radii of $\mathbf{V}_{Aa}^{aa}$ and $\mathbf{V}_{Aa}^{AA}$, respectively. If

$$\rho_{Aa}^{aa} > \bar{w}_{aa}, \qquad [13a]$$

then allele A is protected from loss near $\hat{p}_\alpha^{aa}$, and if

$$\rho_{Aa}^{AA} > \bar{w}_{AA}, \qquad [13b]$$

then allele a is protected from loss near $\hat{p}_\alpha^{AA}$. If both **13a** and **13b** hold for all solutions $\hat{p}_\alpha^{aa}$ and $\hat{p}_\alpha^{AA}$ of **11a** and **11b**, then there is a protected polymorphism.

Gene–Culture Association

That the evolutionary trajectories of phenotypes and genotypes cannot in general be separated is clear from Eqs. **4** and **7**. Under the assumption of genotype-independent transmission, however, Eq. **4** describes purely phenotypic evolution, and Eq. **7** purely genotypic evolution, provided that the phenogenotype frequencies $P_\alpha(i)$ may be factored: $P_\alpha(i) = P_\alpha P(i)$. Departures from this equality have previously been called *gene–culture disequilibrium* (26) by analogy with linkage disequilibrium in population genetics. For more general applicability, it seems appropriate to use the terminology *phenogenotypic association*, $\tilde{\mathcal{A}}_\alpha(i)$, with

$$\tilde{\mathcal{A}}_\alpha(i) = P_\alpha(i) - P_\alpha P(i). \qquad [14]$$

Two other measures of phenogenetic dependence arise naturally. One is *phenogametic* association, $\mathcal{A}_\alpha(i)$, with

$$\mathcal{A}_\alpha(i) = p_\alpha(i) - p_\alpha p(i). \qquad [15]$$

In the case of a single locus where i in Eq. **15** refers to the allele number, $\mathcal{A}_\alpha(i)$ is a *phenoallelic* association. In all cases, if one of the equalities **14** or **15** fails, then the appropriate kind of association exists. It is easy to see that the absence of phenogenotypic association, $\tilde{\mathcal{A}}_\alpha(i) = 0$, entails the absence of phenogametic association—i.e., $\mathcal{A}_\alpha(i) = 0$, which in turn implies absence of phenoallelic association. The reverse set of implications is false. The conditions on selection and transmission under which these associations might vanish are of evolutionary and statistical interest.

Multiplicative selection with genotype-independent transmission. Consider the case of genotype-independent transmission. Suppose again that the only genotype that affects an offspring's viability is its own, and write this genotype in gametic form, $w_{rs}^{\alpha\beta\gamma}$. Return to the phenogametic recursions **9** and rewrite them in terms of gametic, phenotypic, and association values as follows:

$$\bar{w}p'(t) = \sum_{rs}\sum_{\alpha\beta\gamma} \tilde{w}_{rs}^{\alpha\beta\gamma}\Gamma\{rs \to t\}\{\mathcal{A}_\alpha(r) + p_\alpha p(r)\} \times \{\mathcal{A}_\beta(s) + p_\beta p(s)\} \qquad [16a]$$

$$\bar{w}p'_\gamma = \sum_{rst}\sum_{\alpha\beta} \tilde{w}_{rs}^{\alpha\beta\gamma}\{\mathcal{A}_\alpha(r) + p_\alpha p(r)\}\{\mathcal{A}_\beta(s) + p_\beta p(s)\} \qquad [16b]$$

$$\bar{w}\mathcal{A}'_\gamma(t) = \sum_{rs}\sum_{\alpha\beta} \tilde{w}_{rs}^{\alpha\beta\gamma}\Gamma\{rs \to t\}p_\alpha(r)p_\beta(s) - \bar{w}p'(t)p'_\gamma. \qquad [16c]$$

The fitness is FG-*multiplicative* if

$$w_{rs}^{\alpha\beta\gamma} = w_{rs}w^{\alpha\beta\gamma}, \qquad [17]$$

where w_{rs} is a fitness factor associated with (g_r/g_s). It follows that $\tilde{w}_{rs}^{\alpha\beta\gamma} = w_{rs}\tilde{w}^{\alpha\beta\gamma}$, where $\tilde{w}^{\alpha\beta\gamma} = [w^{\alpha\beta\gamma}T\{\alpha\beta \to \gamma\} + w^{\beta\alpha\gamma}T\{\beta\alpha \to \gamma\}]/2$. We then have the following result.

Result 5. Assume that the transmission is genotype-independent and the selection is *FG*-multiplicative. Suppose that $p^*(t)$ and p_γ^* are exponentially locally stable equilibria of Eqs. **18a** and **18b** below, respectively. Then $\{p^*(t), p_\gamma^*\}$ with $p_\gamma^*(t) = p^*(t)p_\gamma^*$ is an isolated locally stable equilibrium of the system **16**:

$$\bar{w}_1 p'(t) = \sum_{rs} w_{rs}\Gamma\{rs \to t\}p(r)p(s) \qquad [18a]$$

$$\bar{w}_2 p'_\gamma = \sum_{\alpha\beta} \tilde{w}^{\alpha\beta\gamma}p_\alpha p_\beta. \qquad [18b]$$

Here $\bar{w}_1 = \Sigma_{rs}w_{rs}p(r)p(s)$ and $\bar{w}_2 = \Sigma_{\alpha\beta\gamma}\tilde{w}^{\alpha\beta\gamma}p_\alpha p_\beta$ are the marginal gametic and phenotypic mean fitness, respectively, and $\bar{w} = \bar{w}_1\bar{w}_2$.

In the absence of selection, we have the following result.

Result 6. Suppose that there is no selection—i.e., $w_{st}^{\alpha\beta\gamma} = 1$ for all s, t, α, β, γ—and that the transmission is genotype-independent. Let $\{p_\gamma^*\}$ be a stable equilibrium of Eq. **18b**. Then in some neighborhood of $\{p_\gamma^*\}$ there is a stable equilibrium of system **16** with $\mathcal{A}_\gamma(t) = 0$ for all γ and t.

Remark. Under the conditions of *Results 5* and *6*, the asymptotic rate of convergence of $\mathcal{A}_\alpha(i)$ to 0 is at least as fast

as $(1/2)^\tau$, where τ is the generation number. In general, the rate at which gamete and phenotype frequencies approach equilibrium is much slower than this. Thus, in the neighborhood of a stable state with $\mathcal{A}_\alpha(i) = 0$, the dynamics of the system may be approximated by the separate Eqs. **18a** and **18b** in the gamete and phenotype frequencies.

FG-*epistatic selection*. In order for $\mathcal{A}_\alpha(i) = 0$ to hold for all α and i, delicate restrictions are required on the fitnesses and transmission rule. Small deviations from these will result in phenogenotypic associations even in the case of one locus. Here we consider a perturbation away from the *FG*-multiplicative case of the form

$$w_{rs}^{\alpha\beta\gamma} = w_{rs}^0 + \varepsilon v_{rs}^{\alpha\beta\gamma}, \qquad [19]$$

where ε is a small parameter. Referring back to Eq. **9a**, define $\phi_{rst}^{\alpha\beta\gamma} = \tilde{v}_{rs}^{\alpha\beta\gamma}\Gamma\{rs \to t\}$, where $\tilde{v}$ is defined in terms of v analogously to $\tilde{w}$ in Eq. **9a**. Then write

$$E_{rst}^{\alpha\beta\gamma} = \phi_{rst}^{\alpha\beta\gamma} - p^*(t)\sum_u \phi_{rsu}^{\alpha\beta\gamma} - p_\gamma^* \sum_\delta \phi_{rst}^{\alpha\beta\delta} + p_\gamma^* p^*(t) \sum_{u\delta} \phi_{rsu}^{\alpha\beta\delta}. \qquad [20]$$

We have then the following result.

Result 7. Consider a single locus and suppose that transmission is genotype-independent. Let $p^*(t)$ $(t = 1, 2, \ldots, n)$ and p_γ^* $(\gamma = 1, 2, \ldots, m)$ be asymptotically locally stable equilibria of Eqs. **18a** and **18b**, respectively, under genotypic selection, $w_{rs}^{\alpha\beta\gamma} = w_{rs}^0$. Thus, $p_\gamma^*(t) = p_\gamma^* p^*(t)$. Then the phenoallelic association at equilibrium of Eq. **16c** with fitnesses given by Eq. **19** is determined by

$$E_\gamma(t) = \varepsilon \sum_{rs}\sum_{\alpha\beta} E_{rst}^{\alpha\beta\gamma} p^*(r)p^*(s)p_\alpha^* p_\beta^* \quad \text{for} \quad \begin{Bmatrix} 1 \le t \le n \\ 1 \le \gamma \le m \end{Bmatrix}, \qquad [21]$$

provided that ε is small.

Thus, deviations from multiplicativity of order ε result in phenogametic associations of the same order. The form of expression **20** as it appears in Eq. **21** demonstrates that maintenance of phenogametic associations demands a kind of epistasis in generalized fitnesses between phenotypes and genotypes. We call it FG-*epistasis*.

Even if the association of phenotypes with genotypes, gametes, or alleles is transient, its presence may affect components of a trait that are not under direct selection. To see this, return to the one-locus case and Eq. **10** under phenotypic selection with genotype-independent transmission. Then Eq. **10** may be written, after summation over γ,

$$p'(t) = p(t) + \sum_\alpha V_\alpha \mathcal{A}_\alpha(t), \qquad [22]$$

where $V_\alpha = [\Sigma_{\beta\gamma}\tilde{w}^{\alpha\beta\gamma}p_\beta]/[\Sigma_{\alpha\beta\gamma}\tilde{w}^{\alpha\beta\gamma}p_\alpha p_\beta]$. Thus, allele frequencies will change if, for some γ, t, $\mathcal{A}_\gamma(t) \neq 0$. This may be surprising, since the selection here is purely phenotypic and the transmission is genotype-independent. Only when the phenotypic selection depends on the offspring alone, and not on the phenotypes of its parents—i.e., $\tilde{w}^{\alpha\beta\gamma} = \tilde{w}^\gamma$—does Eq. **22** reduce to $p'(t) = p(t)$ so that allele frequencies are constant over time.

Concluding Remarks

The evolutionary dynamics of phenotypes in populations, even under some of the constraints on transmission and selection described here, are obviously more complex than either purely genetic or purely phenotypic evolution. It is no surprise that when transmission is genotype-dependent, the evolution of phenotypes and genotypes cannot be separated. Our measures of association between phenotypes and genotypes, gametes, or alleles, the analogs of linkage disequilibrium in population genetics, determine the extent of this interaction. Statistical estimates of the relationship between phenotype and genotype must also be affected by these associations.

Even when transmission is genotype-independent and selection is purely phenotypic, transient phenogenotypic associations cause allele, gamete, and genotype frequencies to change. When selection is *FG*-epistatic, the extent of association at equilibrium can, in special cases, be related to the amount of epistasis. As with linkage equilibrium in classical population genetics, the challenge remains to develop more general theory that relates *FG* epistasis to the extent of phenogenotypic association.

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