Evolution, 45(3), 1991, pp. 630–648

GENETIC COVARIANCE OF FITNESS CORRELATES: WHAT GENETIC CORRELATIONS ARE MADE OF AND WHY IT MATTERS

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Abstract.—The genetic variance-covariance matrix, **G**, is determined in part by functional architecture, the pathways by which variation in genotype influences phenotype. I develop a simple architectural model for **G** for two traits under directional selection constrained by their dependence on a common limiting resource. I assume that genetic variance is maintained by mutation-selection balance. The relative numbers of loci that play a role in acquiring versus allocating a limiting resource play a crucial role in determining genetic covariance. If many loci are involved in acquiring a resource, genetic covariance may be either negative or positive at equilibrium, depending on the fitness function and the input of mutational variance. The form of **G** does not necessarily reveal the constraint on resource acquisition inherent in the system, and therefore studies estimating **G** do not test for the existence of life-history tradeoffs. Characters may evolve in patterns that are unpredictable from **G**. Experiments are suggested that would indicate if this model could explain observations of positive genetic covariance.

Key words.—Evolutionary constraint, life history, quantitative genetics.

Received May 23, 1990. Accepted August 14, 1990.

In the past 10 years, it has been argued that the genetic variance covariance matrix is of some fundamental importance in shaping the evolutionary potential of populations (Lande, 1979, 1982; Cheverud, 1982, 1984; Maynard Smith et al., 1985; Clark, 1987*a*). One area where this concept has taken root is in the study of life-history characters, where the limitations on their evolution are expected to be reflected in negative genetic covariances (Lande, 1982; Reznick, 1985; Bell and Koufopanou, 1986; Charnov, 1989).

Such interest has focussed attention on the processes that potentially shape genetic covariances. As with genetic variances, either mutation-selection balance or balancing selection could explain their maintenance (Barton, 1990). There is ample evidence that at least some genetic variance and covariance is maintained by mutation-selection balance (Crow and Simmons, 1983; Charlesworth, 1987; Kondrashov, 1988; Barton and Turelli, 1989; Barton, 1990). This, plus its conceptual simplicity has made mutation-selection balance a favorite basis for models of variance and covariance. The mutation model used for much of this work is that of a single locus capable of producing the full range of pleiotropic effects on phenotypes. The effects of alleles are then assumed to follow some multivariate distribution, with given covariance. Then genetic covariances will similarly depend on the balance between the input of mutational covariance and the power of selection to reshape it (Lande, 1980; Turelli, 1985; Clark, 1987*a*). This approach has been useful in exploring many issues raised by the mutation-selection balance model.

Alternatively, one may build a mutation model based on the assumption that there is more than one type of locus, each with a fixed pattern of pleiotropic allelic effects. This reflects the well-known fact that individual loci have very specific roles, usually restricted to a single metabolic or developmental pathway. These sets of pathways form the underlying *functional architecture* that determines the pattern of pleiotropic effects. In this approach, each locus affects only one fundamental, usually unobserved, character. The genetic vari-

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ance-covariance matrix (**G**) we then observe is a function of the genetic variance in fundamental characters, and functional architecture. Wagner (1989) has presented an elegant linear model of this type. Similar approaches have also been applied to pairs of morphological characters (Riska, 1986; Slatkin, 1987).

In this paper, I will explore the consequences of adopting an architectural model for characters under directional natural selection, which I will refer to as fitness correlates. Such characters will not have their equilibrium means determined by selection alone, as no character can increase without limit. One reasonable source of constraint on fitness correlates is the ability of the organism to acquire limiting "resources," such as carbon, time, or space. The way in which the organism allocates these resources to different characters then determines the phenotype. The architectural model is a convenient framework for studying the covariance of directionally selected characters, as constraints on acquisition may be incorporated in a straightforward fashion.

There are two ways that **G** can reflect evolutionary constraints. First, characters may have little additive variance. A large number of experiments have now shown that this is rarely, if ever, the case (Istock, 1983; Roff and Mousseau, 1987; Mousseau and Roff, 1987). Second, the pattern of covariance among characters may be such that segregating alleles that increase one fitness correlate have antagonistic effects on other fitness correlates. This leads to the prediction of negative genetic covariance between fitness correlates (e.g., Lande, 1982). The logic of this is that alleles that have positive pleiotropic effects on sets of characters will be fixed rapidly, those with negative effects will be lost, while those that affect some traits positively and others negatively will tend to remain at intermediate frequencies longer. This prediction of negative genetic covariance has been taken so seriously that some authors have claimed that positive genetic covariances would challenge current theories of life history evolution (Reznick et al., 1986; Rose, 1984; Scheiner et al., 1989).

However, the definition of constraints that leads to the view that **G** will reflect them is a very weak one. Clark (1987*a*), for example, defines a constraint as "those aspects of the inheritance of traits that prevent natural selection from resulting in the steepest ascent approach of the mean phenotype to the optimum." Clearly, most forms of **G** constitute a constraint in this sense (Lande, 1979). However, the definition of constraint more appropriate to fitness correlates is that which prevents, rather than delays, the attainment of phenotypes favored by selection. Unless **G** takes a rather extreme form, for example correlations of $+1$ or -1 (e.g., Via and Lande, 1985), one will be unable to determine from examination of **G** whether all variation is in fact constrained by pleiotropic effects. Evolution will still occur if even a single locus with transient effects on **G** is capable of mutation to beneficial alleles. The question of whether **G** reflects constraints is distinct from that of whether constraints exist.

In keeping with this, competent estimates of covariances for fitness correlates are as likely to be positive as negative (e.g., Rose and Charlesworth, 1981; Hegmann and Dingle, 1982; Bell, 1984*a*, 1984*b*; Yoshimaru and Mukai, 1985; Mitchell-Olds, 1986; Futuyma and Philippi, 1987; Garland, 1988; Billington et al., 1988; Rausher and Simms, 1989; Clark, 1990). The interpretation of such results is contentious, as there is an extensive catalog of factors that can lead to spuriously high estimates of covariances (Rose, 1984; Reznick, 1985; Reznick et al., 1986; Bell and Koufopanou, 1986; Clark, 1987*b*). This has led to the suggestion that costs of reproduction are better demonstrated through interpopulation correlations or experimental manipulations, which do seem to reflect costs in the majority of studies (Reznick, 1985; Bell and Koufopanou, 1986; Partridge and Harvey, 1988).

The one potential explanation for positive additive genetic correlations that has not received much attention is that they may in fact be positive at equilibrium. I will show that when mutation-selection balance is responsible for the maintenance of genetic variance there are circumstances where positive additive covariance is expected at equilibrium. I model an organism whose fitness is completely determined by two fun-

damental, unobserved characters: the amount of limiting resource it acquires and the way it allocates that resource to observed characters. Variation in allocation generates negative covariance, while variation in acquisition generates positive covariance between the observed characters, and the overall sign of the covariance is determined by the relative magnitudes of the two covariances. I assume a simple "functional architecture" where loci affect either acquisition or allocation, but not both. This assumption is obviously to some degree unrealistic, but may conform more closely to the actual situation than assuming all loci are equivalent. By explicitly considering architecture, I can explore intuitively reasonable assumptions about the mutational sources of covariance. I will focus on the relative numbers of loci that potentially affect allocation and acquisition as a principal determinant of mutational covariance.

Elements of this basic idea have been discussed by other authors. The possibility that deleterious alleles make a substantial contribution to genetic covariance is widely mentioned (e.g., Falconer, 1981 pp. 306–307). Van Noordwijk and de Jong (1986) suggested the acquisition-allocation dichotomy as an explanation for positive phenotypic covariance. Bell and Koufopanou (1986) placed this idea in a more genetic context, and used it to argue that nonequilibrium populations should have higher genetic covariance than equilibrium ones. Charlesworth (1990) has shown generally that negative covariance is never necessary even when the population is at an optimum. He also shows that mutation could supply enough positive covariance to swamp the predominant pattern of negative covariance favored by selection.

To organize these results I will focus on determining the ratio of the numbers of acquisition and allocation loci that would lead to an expectation of no covariance between a pair of characters under directional selection. I call this ratio the "zero covariance architecture" (ZCA). This reduces the question of whether such a model can explain observations of positive covariance to whether it is likely that the ratio of acquisition to allocation loci could be as large as the ZCA.

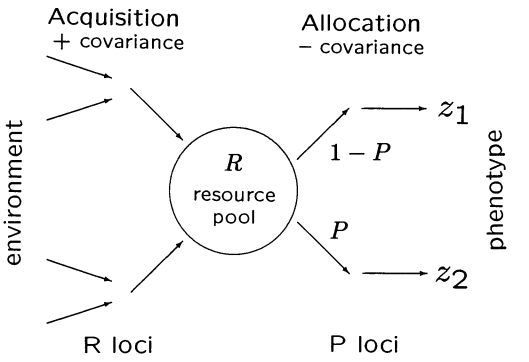

FIG. 1. The functional architecture of resource acquisition and allocation. Arrows represent loci that affect acquisition or allocation.

THE MODEL

I consider a pair of traits, z_1 and z_2, which are under directional selection. The vector **z** consists of the phenotypes z_1 and z_2, of these two traits. The variation in **z** is due to genetic and environmental effects. Phenotypic, environmental, and genetic variances and covariances will be symbolized $T \ldots$, $E \ldots$, and $G \ldots$ respectively. I assume throughout an infinite random-mating diploid population at gametic-phase equilibrium, no epistatic interactions, and no genotype-environment correlations or interactions.

Genetic Architecture

I assume that **z** is determined by two fundamental variables: R, the amount of resource the organism acquires, and P, the proportion of those resources allocated to z_2. Loci that affect **z** do so either by affecting the acquisition of resources from the environment (R loci) or by affecting the allocation of acquired resources to traits (P loci). This resource-based functional architecture is represented in Figure 1. Then

$$z_1 = R(1 - P) \quad \text{and} \quad z_2 = RP. \tag{1}$$

The variation in R and P has both a genetic and an environmental component

$$R = \bar{R} + r + \epsilon_r$$

and

$$P = \bar{P} + p + \epsilon_p, \tag{2}$$

where $\bar{R}$ and $\bar{P}$ are means, r and p represent genetic deviations, and ϵs are the environmental deviations in each phenotype.

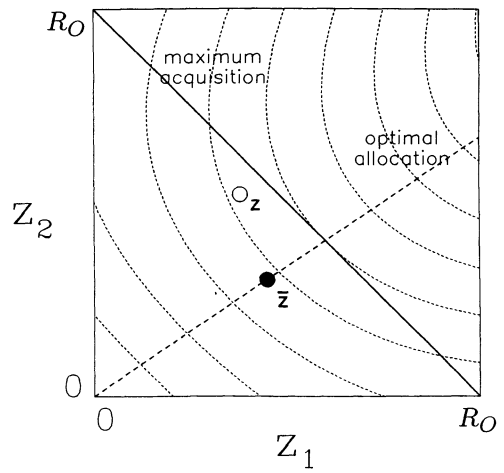

FIG. 2. A representative adaptive surface on which z_1 and z_2 evolve. The curved, dashed lines represent fitness contours, with low fitness at the lower left. Evolution is constrained by the assumption that the expected amount of resource acquired is less than R_o, represented by the heavy diagonal solid line. In this hypothetical case, the population mean, $\bar{z}$ is on a ridge of high fitness whose peak is the dashed diagonal line labeled optimal allocation. The individual z has higher than average fitness because it has above average resource acquisition, the sum of z_1 and z_2, although it has allocated its resources in a proportion far from the optimum.

Selection

I consider two families of fitness functions that share the feature that fitness is a monotonically increasing function of resource acquisition, R, and stabilizing selection on resource allocation, P. Thus selection is primarily directional on both z_1 and z_2. A representative adaptive landscape of this type is shown in Figure 2.

To determine selection coefficients, I assume that allelic effects are small, relative to $\bar{R}$ and $\bar{P}$. Then, following Kimura and Crow (1978), the expected fitness of a genotype with phenotypic effects r_i and p_i is

$$\bar{W}_i = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} W(R + r_i, P + p_i) \cdot F(R, P)\, dR dP. \quad (3)$$

For both R and P loci, selection on genotypes is parameterized using relative genotypic fitnesses of $W_{00} = 1$ for the optimal homozygote, $W_{11} = 1 - s$ for the mutant homozygote, and $W_{10} = 1 - hs$ for their respective heterozygote. The selection coefficient against allele 1 is

$$s = (\bar{W}_{00} - \bar{W}_{11})/\bar{W}_{00}, \quad (4)$$

and its dominance for fitness is

$$h = (\bar{W}_{00} - \bar{W}_{10})/(\bar{W}_{00} - \bar{W}_{11}). \quad (5)$$

Maintenance of Genetic Variance

I assume that genetic variance at R and P loci is maintained by mutation-selection balance. Alleles have additive effects on phenotypes R and P.

I model the variance at acquisition, or R loci using a standard two allele model of mutation-selection balance. I assume that there are n_r identical acquisition loci, which undergo reversible mutation at rate μ_r. Mutant alleles always decrease the acquisition of resources by an amount a_r. When the dominance for fitness, h_r, is not 1/3, the equilibrium frequency of a mutant allele is

$$\hat{q}_r \approx \frac{(h_r s_r + 2\mu_r - \sqrt{(h_r + 2\mu_r)^2 + 4\mu_r s_r(3h_r - 1)})}{2s_r(3h_r - 1)}, \quad (6)$$

and when $h_r = 1/3$,

$$\hat{q}_r \approx \frac{3\mu_r}{s_r + 6\mu_r}, \quad (7)$$

assuming that $\hat{q} \ll 1$. The genetic variance in acquisition is

$$G_R = 2n_r\hat{q}_r(1 - \hat{q}_r)a_r^2. \quad (8)$$

I assume that there is a maximum amount of resources that a population may be expected to accumulate

$$R_o \geq \bar{R}. \quad (9)$$

The realized mean is

$$\bar{R} = R_o - 2n_r\hat{q}_r a_r H, \quad (10)$$

where H is the "hardness" of genotypic effects. H expresses the degree to which segregation of deleterious alleles reduces the population mean, and ranges from 0 to 1. If $H = 1$, the expected amount of resource an individual acquires is determined absolutely by its genotype, and genotypic effects are "hard." If $H = 0$, only the relative ability to acquire resources is affected, the population mean will be unaffected by mutant alleles, and genotypic effects are "soft."

When $H > 0$, equations (4) and (10) must be solved simultaneously or iteratively to obtain $\bar{R}$ and s_r. Figure 2 represents a hard selection case, since the mean level of resource acquisition is less than R_o.

Genetic variance at the allocation, or P, loci is modeled using a three allele model (Turelli, 1984). I chose a three allele model to emphasize that both mutations that increase and those that decrease P are allowed, unlike those affecting R. The three alleles, Y_{+1}, Y_0, and Y_{-1} have effects a_p, 0, and $-a_p$, respectively on the phenotype. I assume that the population has evolved so that $\bar{P}$ maximizes mean fitness. For the symmetrical fitness functions I assume, this assures that the expected fitnesses of Y_{+1}, and Y_{-1} are equal. Mutation between the three alleles depends on the rate μ_p, and obeys the following scheme:

$$Y_{-1} \underset{\mu_p/2}{\overset{\mu_p}{\rightleftharpoons}} Y_0 \underset{\mu_p}{\overset{\mu_p/2}{\rightleftharpoons}} Y_{+1}.$$

There are n_p identical allocation loci. The equilibrium frequency of the nonoptimal alleles 1 and -1 is

$$\hat{q}_p \approx \frac{(2\mu_p + h_p s_p - \sqrt{(s_p h_p + 2\mu_p)^2 - 2\mu_p s_p(6h_p - 1)})}{2s_p(6h_p - 1)}, \quad (11)$$

neglecting terms in $\mu_p s_p$. The equilibrium genetic variance is

$$G_P = 4n_p \hat{q}_p a_p^2. \quad (12)$$

Variance and Covariance of z_1 and z_2

Since z_1 and z_2 are products of R and P, $\mathbf{G}$ is a simple function of the variance and covariance of R and P. Assuming there is no genetic covariance between R and P, the genetic variance-covariance matrix $\mathbf{G}$ has elements

$$G_{11} = (1 - \bar{P})^2 G_R + G_P \bar{R}^2 + G_R G_P \quad (13)$$
$$G_{22} = \bar{P}^2 G_R + G_P \bar{R}^2 + G_R G_P \quad (14)$$
$$G_{12} = \bar{P}(1 - \bar{P}) G_R - G_P \bar{R}^2 - G_R G_P. \quad (15)$$

Standard Parameter Values

To obtain numerical results, I assume a standard set of parameter values, shown in Table 1, and explore the effect of departures from them two variables at a time. Few of the parameters in this model have been well estimated in any population. Mukai's (Mukai et al., 1972) work on viability mutations in *Drosophila melanogaster,* coupled with other work on total fitness effects (Sved, 1971; Sved and Ayala, 1970; Simmons and Crow, 1977; Crow and Simmons, 1983; MacKay, 1986), suggests that the proportional decrease in fitness due to an average polygenic mutation is in the range 0.02–0.08. I will assume effects at the upper end of this range, as the relevant experiments were done in the lab under optimal conditions. I assume that R and P mutations have equal effects, a_2, on z_2, and that $a_r/R_o = a_p/\bar{P} = 0.04$. The environmental variances are chosen so that when $\bar{P} = 0.5$, $\bar{R} = 10$, and the phenotypic covariance $T_{RP} = 0$, the coefficient of variation of z_2 will be approximately the median value for life history characters (Houle, 1991). In addition, I assume that E_R and E_P contribute equally to the environmental variance in z_2. The standard mutation rate is consistent with Kondrashov's (1988) recent review.

Results

Additive Fitness Functions

Pairs of characters such as present and future reproduction are likely to have additive effects on lifetime fitness. Fitness will then depend primarily on $z_1 + z_2 = R$. It does not seem biologically plausible to assume that fitness depends solely on R, so I also assume that there is stabilizing selection on P. Stabilizing selection is represented by a gaussian fitness function so that selection coefficients may be obtained exactly. Any symmetrical stabilizing fitness function would give equivalent results, as gene frequencies in the finite allele model considered depend only on the selection coefficients of nonoptimal alleles (Eqs. 6, 11). Generalizing slightly, suppose that fitness can be written

$$W(R, P) = R^k \exp\left[\frac{-(P - P_o)^2}{2w^2}\right]. \quad (16)$$

When $k < 1$, there are diminishing returns in fitness for increases in R; and when $k >$

TABLE 1. Standard parameter values and notation.

Parameter	Loci	Symbol	Value
Mutation rates	R	μ_r	5×10^{-5}
	P	μ_p	5×10^{-5}
Optimal acquisition	R	R_o	10
Hardness of genotypic effects	R	H	0
Average allelic effect on	R	a_r	0.40
	P	a_p	0.02
Average allelic effect on z_2	R, P	a_2	0.20
Number of loci	R	n_r	
	P	n_p	
Environmental variance of	R	E_R	2.0
	P	E_P	0.005
Genetic variance, covariance		$G\ldots$	
Phenotypic variance, covariance		$T\ldots$	
Selection parameters			
Optimal allocation	P	P_o	0.5
Strength of selection on P	P	w^2	0.4
Exponents		j, k	1.0

1, W is an accelerating function of R. The parameter w^2 determines the strength of stabilizing selection on P for the optimal allocation proportion, P_o.

For most values of k, only approximate numerical results can be obtained. However, if $k = 1$, equation (3) may be solved exactly using (16), after making the assumption that R and P are bivariate normal. This is shown in Appendix A. Since both R and P are bounded ($R > 0$, and $0 \leq P \leq 1$), this requires the additional assumptions that $\sqrt{T_R} \ll \bar{R}$ and $\sqrt{T_P} \ll \bar{P}$ or $\sqrt{T_P} \ll 1 - \bar{P}$, whichever is smaller. This approach also requires $a_r \ll \bar{R}$, $a_p \ll \bar{P}$ and $a_p \ll 1 - \bar{P}$. Overall mean fitness is

$$\bar{W} = \exp\left[\frac{-(\bar{P} - P_o)^2}{2V_s}\right] \cdot \sqrt{\frac{w^2}{V_s}}\left(\bar{R} + \frac{T_{RP}(P_o - \bar{P})}{V_s}\right), \quad (17)$$

where $V_s = T_P + w^2$.

A nonzero phenotypic covariance has an effect on the equilibrium value of $\bar{P}$, but little impact on genetic variances. Differentiating (17) with respect to $\bar{P}$, $\bar{W}$ is maximized when

$$T_{RP} = (P_o - \bar{P})\left(\bar{R} + T_{RP}\frac{P_o - \bar{P}}{V_s}\right). \quad (18)$$

Thus, any phenotypic covariance between R and P will tend to drive $\bar{P}$ away from P_o. If V_s is not small, since $T_{RP} \ll \bar{R}$, condition (18) reduces to

$$\frac{T_{RP}}{\bar{R}} \approx P_o - \bar{P}. \quad (19)$$

The selection coefficient of a genotype j, with an effect p_j on P and no effect on R is

$$s_p \approx \frac{p_j}{V_s}\left(\frac{p_j}{2} + (\bar{P} - P_o) + \frac{T_{RP}}{\bar{R}}\right). \quad (20)$$

The last two terms cancel, so at equilibrium a mutant with effect p_j will have approximately the same fitness regardless of the value of T_{RP}. Similarly, the selection coefficient for a mutant with an effect r_i is

$$s_r = \frac{r_i}{\bar{R} + T_{RP}\dfrac{P_o - \bar{P}}{V_s}} \approx \frac{r_i}{\bar{R}}. \quad (21)$$

Therefore, unless V_s is very small, phenotypic covariance will have little effect on genetic variances or covariances. Further calculations will assume that $T_{RP} = 0$. This considerably simplifies equation (A6), because fitness will be maximized at $\bar{P} = P_o$. Then, the mean fitness of genotype i, with phenotypic effects p_i and r_i is

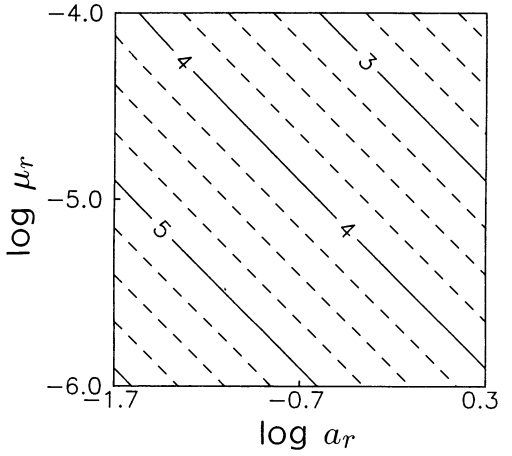

FIG. 3. Contour plot of $\log_{10} n_r$, which is required to generate the amount of genetic variance discussed in the text, as a function of $\log_{10}\mu_r$ and $\log_{10} a_r$. Definitions of parameters, and values used for the parameters not shown are given in Table 1. The contour interval is 0.25. The contour lines on this and the next figure connect pairs of parameter values which require the same number of loci. The numbers on the solid contour lines are the values of $\log_{10} n_r$ required. For example, if $\log_{10} a_r = -0.7$ ($a_r \approx 0.2$), and $\log_{10}\mu_r = -5$ ($\mu_r = 10^{-5}$), then $\log_{10} n_r \approx 4$, and n_r must be about 10,000 to generate a coefficient of variation of 10. If the change in contour for a change in one parameter value remains constant for all values of the other parameter, as it does here, the two parameters on the axes do not interact in determining number of loci. This is the case in this figure. To see what an interaction would look like, see Figure 4.

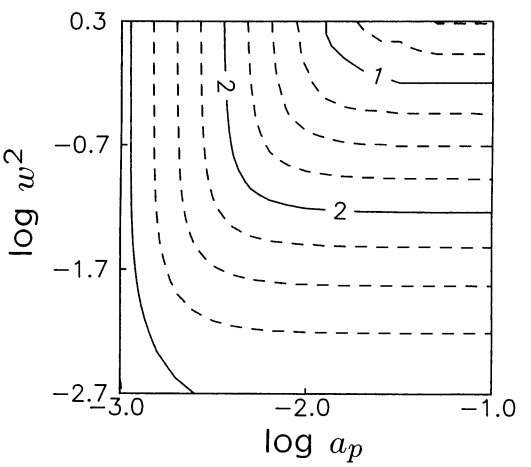

FIG. 4. Contour plot of log n_p required to generate the amount of genetic variance discussed in the text, as a function of log w^2 and a_p. For explanation, see Figure 3. Examination of the figure shows that w^2 and a_p do interact in determining n_p. For example, near the top of the figure a small change in w^2 has no effect on n_p when a_p is small, as shown by the vertical contours in the upper left, and some effect when a_p is large, as shown by the departure of the contours from the vertical.

$$\bar{W}_i = \sqrt{\frac{w^2}{V_s}} \exp\left[\frac{-p_i^2}{2V_s}\right](\bar{R} + r_i). \quad (22)$$

The equilibrium genetic variance in R, G_R, may be obtained by making appropriate substitutions into (5), (7), (8), (10), and (21). This yields

$$G_R \approx \frac{n_r\mu_r a_r R_o}{1 + 2n_r\mu_r H}. \quad (23)$$

Similarly substituting appropriately into (A6), (4), (5), (11), and (12) yields

$$G_P = n_p\Big(4\mu_p V_s + a_p^2 - \sqrt{(4\mu_p V_s)^2 + a_p^4}\Big) \quad (24)$$

One important question is how many R and P loci it would take to generate a typical amount of variance in **z**. Recent reviews of data on life-history characters suggest that a genetic coefficient of variation (e.g., $100\sqrt{G_2}/\bar{z}_2$) of 10, and heritability of 0.2 are approximate median values (Mousseau and Roff, 1987; Roff and Mousseau, 1987; Houle, 1991). Assuming that acquisition and allocation loci each contribute half this variance, how many loci of each kind are necessary under this model? A contour plot of the number of acquisition loci necessary when $\bar{P} = 0.5$ is shown in Figure 3, using the standard parameter values given in Table 1. Many loci, with relatively large effects are clearly necessary, however for values of a_r near the standard value ($log_{10} a_r \approx -0.4$) they are far less than the numbers of loci that are capable of influencing fitness correlates (see Discussion). Clearly for parameter combinations leading to $n_r \gg 10^4$, mutation-selection balance will be unable to maintain the necessary variation.

A contour plot of the number of P loci necessary is shown in Figure 4. Clearly, relatively few P loci are necessary to maintain measurable genetic variance (cf. Turelli, 1984). When $a_p^2/w^2 \approx s_p \gg \mu_p$, the model shows the insensitivity to a_p, which leads to the "rare alleles" approximation for the continuum of alleles model (Turelli, 1984; Barton and Turelli, 1987). When w^2 is very

large, however, selection becomes weaker than mutation and all three alleles in the model become equally common. This upper limit to genetic variance would not occur in a true continuum of alleles model.

Finally, substituting (23) and (24) into (15), yields a condition for the genetic covariance, G_{12}, to be zero

$$\frac{n_r}{n_p} = \frac{R_o\left(4\mu_p V_s + a_p^2 - \sqrt{(4\mu_p V_s)^2 + a_p^4}\right)}{(1 + 2n_r\mu_r H)\left(a_r\mu_r\bar{P}(1 - \bar{P})\right)}. \tag{25}$$

I define the ratio, n_r/n_p, which satisfies such an equation the "zero covariance architecture," or ZCA. If n_r/n_p is larger than the ZCA, then the equilibrium covariance will be positive. One interesting feature of equation (25) is that increasing the hardness of genetic effects actually decreases the ZCA. The decrease in G_R as hardness increases is more than offset by the decrease in $\bar{R}^2$, which determines the contribution of G_P to G_{12} (equation 15). The change in ZCA due to hardness will be small as long as $n_r \ll 1/\mu_r$, so additional results assume $H = 0$.

Then, when the rare alleles approximation applies, for soft genetic effects ($H = 0$), the ZCA reduces to

$$\frac{n_r}{n_p} \approx \frac{2\mu_p V_s R_o}{a_r\mu_r\bar{P}(1 - \bar{P})}. \tag{26}$$

I have already assumed that $a_r \ll \bar{R}$, and in effect that V_s is within an order of magnitude of $\bar{P}(1 - \bar{P})$. Therefore, assuming that the mutation rates are of the same order, the ZCA will be greater than 1, with most likely values being in the neighborhood of 100 (for instance, using the parameter values in Table 1). The largest source of uncertainty is in the value of w^2, which determines the strength of selection on P, for which no empirical estimates for allocation of resources are available. The value chosen as a point of departure in Table 1 is justified only in that it fulfills the order assumptions used to obtain (26), and corresponds to the strength of selection on some morphological characters (Turelli, 1984).

A broader range of parameters may be explored numerically by returning to the less restrictive assumptions used to obtain (22). For example, Figure 5 shows a contour plot of log(ZCA) as a function of the effects of mutants at R and P loci. As expected, larger average effects generally translate into larger genetic variances for the appropriate phenotype, except where the "rare alleles" approximation applies for P loci, in the upper half of the figure.

Figure 6 shows ZCA as a function of s_p, determined by changing w^2, and s_r as a function of R_o. Like V_s for P loci, R_o directly determines the strength of selection at R loci (see equation 21). G_P is proportional to s_p as expected, since $s_p \gg \mu_r$. The surprise is that *increasing* s_r by decreasing R_o actually *decreases* the ZCA. The reason is that G_R is proportional to R_o, while the contribution of G_P to G_{12} is proportional to R_o^2 (see Eq. 15).

When $k \neq 1$, equation (16) may be approximated using a Taylor expansion by making the assumptions that $w^2 \gg T_P$ ($V_s \approx w^2$), $\bar{R}$ is of order 1 or larger, and that $\bar{R} \gg k$. Taking expectations over R and P for a genotype with effects r_i and p_i and in such an expansion,

$$\begin{aligned}\bar{W}_i \approx \bar{R}^k \exp\left[\frac{-(\bar{P} - P_o)^2}{2w^2}\right] \cdot \Bigg(1 &+ r_i\frac{k}{\bar{R}} + p_i\frac{(P_o - \bar{P})}{w^2} \\ &+ (r_i^2 + T_R)\frac{k(k-1)}{2\bar{R}^2} \\ &+ (p_i r_i + T_{RP})\frac{k(P_o - \bar{P})}{\bar{R}w^2} \\ &- \frac{p_i^2 + T_P}{2w^2} - p_i T_{RP}\frac{k}{\bar{R}w^2}\Bigg),\end{aligned} \tag{27}$$

where all terms of order $\bar{R}^k(a_p^2/w^2)$ or larger are retained. Numerical results not shown suggest that T_{RP} has a negligible impact on ZCA when $k \neq 1$, like when $k = 1$. I plot the ZCA as a function of k and the average effect of a mutation in Figure 7. As expected, k has a large impact on the ZCA. In spite of the curious shape of the contours, there is in fact no interaction between k and a_2. The contours bend because I assume that $a_r\bar{P} = a_p\bar{R} = a_2$. Moving vertically in Figure 7 is equivalent to moving from lower left to upper right in Figure 5. Results not shown also suggest that there is no interaction be-

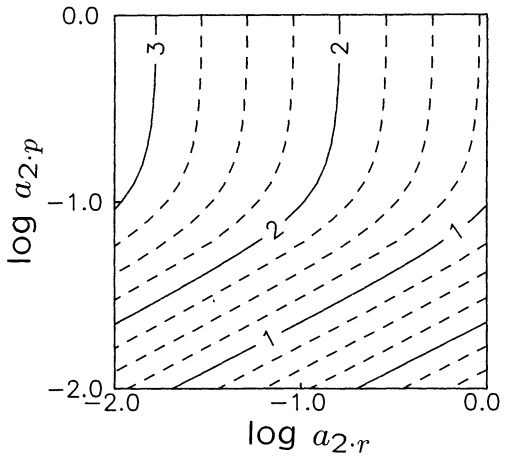

FIG. 5. Contour plot of log zero covariance architecture (ZCA) for the additive selection case. ZCA is the ratio n_r/n_p necessary for there to be no covariance between z_1 and z_2 at equilibrium. ZCA is shown as a function of log $a_{2\cdot r}$ and log $a_{2\cdot p}$, where a_2 . . . is the average effect of a mutation at an R or P locus, respectively, on z_2. The contour interval is 0.25. The contour lines on this and subsequent figures connect pairs of parameter values that lead to the same ZCA. The numbers on the solid contour lines are the values of $\log_{10}$ZCA predicted. For example, if $\log_{10}a_{2\cdot r} = \log_{10}a_{2\cdot p} = -1.0$ ($a_{2\cdot\cdot} = 0.1$), then $\log_{10}$ZCA ≈ 2, and n_r/n_p must be about 100 for there to be no covariance between z_1 and z_2.

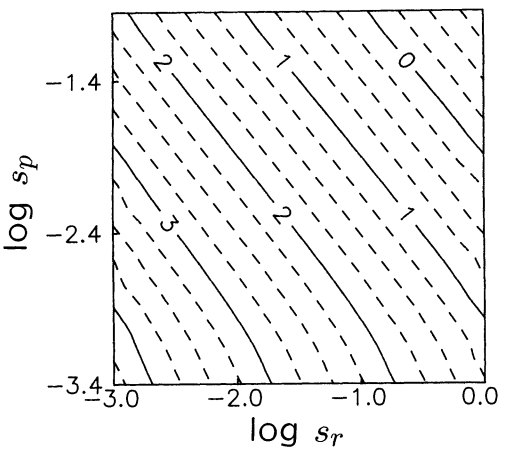

FIG. 6. Log ZCA as a function of the logged selection coefficients, for the additive selection case. s_r varies as a function of R_o, and s_p varies as a function of w^2. For an explanation of the plot, see Figure 5. In order for s_p to be larger than shown here, E_P would have to be reduced.

tween k and any other parameters in determining ZCA, so the effects of the parameters in Figures 3–6 also occur when $k \neq 1$.

Multiplicative Fitness Functions

Many pairs of life-history traits will jointly have a multiplicative effect on fitness, such as viability and fecundity, or offspring number and offspring quality. Such fitness functions may be represented

$$W(R, P) = z_1^j z_2^k = R^{j+k}P^k(1 - P)^j. \quad (28)$$

The optimal allocation proportion will always be greater than 0 and less than 1, but its numerical value will depend on j and k. Multiplicative fitnesses generate stabilizing selection on P without the imposition of additional constraints, as was necessary in the additive case.

As in the additive case, when $j = k = 1$, (28) may be used to solve (3) exactly. This is shown in Appendix B. From (A12) one can see that mean fitness is maximized when

$$\bar{P} \approx \frac{\bar{R} - 4T_{RP}}{2\bar{R}}. \quad (29)$$

At equilibrium, $\bar{P} = 1/2$ when $T_{RP} = 0$, and very close to 1/2 when it is not, as $\bar{R} \gg T_{RP}$. Similarly, in the selection coefficients for mutants at R and P loci, terms involving T_{RP} can all be dropped as insignificant compared to the dominant terms in $\bar{R}$. Therefore, I will assume that $T_{RP} = 0$.

The resulting selection coefficients are

$$s_p = 16p_j^2 \quad \text{and} \quad s_r = \frac{-4r_i}{\bar{R}}. \quad (30)$$

Comparison with (20) and (21) shows that selection on genotypes that affect R is doubled from the additive case when $k = 1$. Selection on genotypes which affect P in the multiplicative case is equivalent to the additive case when $V_s = 1/8$. This is about a threefold increase over the arbitrary standard value I used for V_s above. Maintaining genetic variance will require correspondingly more R and P loci than suggested in Figures 3 and 4. As in the additive case, if mutation is a weak force the ZCA can be approximated

$$\frac{n_r}{n_p} = \frac{2\bar{R}\mu_p}{\mu_r a_r(1 + 2n_r\mu_r H)}. \quad (31)$$

When genetic effects are soft, $H = 0$, the ZCA will be approximately 50 for my standard parameter values, somewhat less than

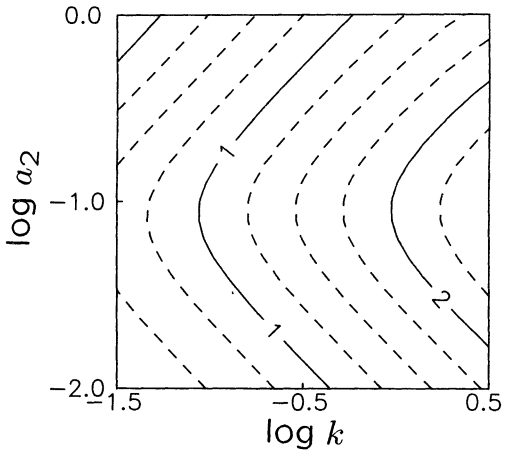

FIG. 7. Log(ZCA) as a function of the exponent k and a_2, for the additive selection case. The average effects of R and P loci on z_2 are assumed to be equal, so $a_2 = \bar{P}a_r = \bar{R}a_p$. For an explanation of the plot, see Figure 5.

for the additive case. Only the relative mutation rates, and the ratio $\bar{R}/a_r$ will influence (31), so the range of possible ZCA values emerging from the multiplicative selection case is much narrower than that for the additive. Otherwise, the two selection functions result in surprisingly similar ZCA values.

As in the additive case, a Taylor approximation was used to evaluate equation (28) when the exponents j and k are not both equal to 1. To do this I assume that R and P have symmetrical distributions, $\bar{R} > 1$, and $\bar{R} \gg j + k$, so that only terms to third order make large contributions. The resulting expression is shown in Appendix C. The value of $\bar{P}$ that maximized (A13) was found numerically. This equilibrium value of $\bar{P}$ depends primarily on the exponents j and k. When $j = k$, $\bar{P} = 0.5$, but when j and k are very unequal, $\bar{P}$ approaches 1 or 0. The three allele model is built on the assumption of symmetry of genetic effects and the phenotypic distribution of P, which cannot apply in such cases without a modification, such as a scale transformation. Figure 8 presents the ZCA surface as a function of j and k, avoiding combinations where $\bar{P}$ is within two phenotypic standard deviations of 1 or 0. The apparent asymmetry is an artifact of determining k relative to j. Numerical results not shown suggest that there are no interactions between other parameters and j and k.

More Characters

When more characters are studied, it becomes increasingly difficult to make predictions about covariances. An intuitively reasonable expectation for genetic covariances among three or more characters is that characters that share more functional architecture should have larger genetic correlations. In Figure 9, I show an architecture for three measured characters, z_1, z_2, and z_3, and three unmeasured ones, R, P_1, and P_2. The naive expectation is the z_2 and z_3 will covary more positively than either will with z_1. The expected covariances G_{12}, G_{13}, and G_{23} are easily obtained as the covariances of products of the unmeasured variables. For the sorts of parameter values used above, products of genetic variances may be ignored, leaving

$$\begin{aligned} G_{12} &\approx (1 - \bar{P}_2)\,((1 - \bar{P}_1)\bar{P}_1 G_R - \bar{R}^2 G_{P1}) \\ G_{13} &\approx \bar{P}_2((1 - \bar{P}_1)\bar{P}_1 G_R - \bar{R}^2 G_{P1}) \\ G_{23} &\approx \bar{P}_2(1 - \bar{P}_2)(\bar{P}_1^2 G_R + \bar{R}^2 G_{P1}) \\ &\quad - \bar{P}_1^2 \bar{R}^2 G_{P2} \end{aligned} \tag{32}$$

$$\begin{aligned} &G_{23} > G_{12} \text{ if} \\ &\bar{R}^2(G_{P1}(2\bar{P}_2 - \bar{P}_2^2) - \bar{P}_1^2 G_{P2}) \\ &\quad - G_R \bar{P}_1 \bar{P}_2(1 - \bar{P}_1(2 - \bar{P}_2)) > 0. \end{aligned} \tag{33}$$

This condition is readily violated if G_R is large and allocation proportions are near 0.5, as in the two character cases above. In addition, it will also be violated if G_{P2} is large relative to G_{P1}. For example, if $\bar{P}_1 = \bar{P}_2 = 0.5$, (33) cannot be satisfied if $G_{P2} > 3G_{P1}$, regardless of the size of the acquisition variance. This could occur if the number of loci affecting P_2 is larger than that affecting P_1, or if stabilizing selection is stronger on P_1 than P_2.

DISCUSSION

In this model, both the signs and relative magnitudes of equilibrium additive covariances among resource-limited fitness correlates depend on the underlying functional architecture of the loci that determine the phenotype. For the simple architecture considered, a principal determinant of genetic covariance is the relative numbers of loci

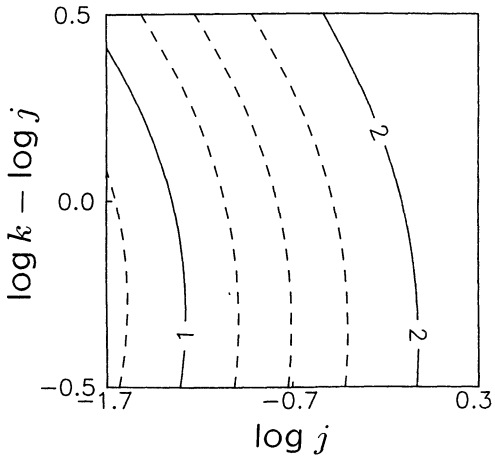

FIG. 8. Log(ZCA) as a function of exponents j and k in the multiplicative fitness case. If j and k are very unequal, $\bar{P}$ will be too close to the boundaries 1 or 0 for the approximation used to hold. Therefore, k is varied relative to j. For an explanation of the plot, see Figure 5.

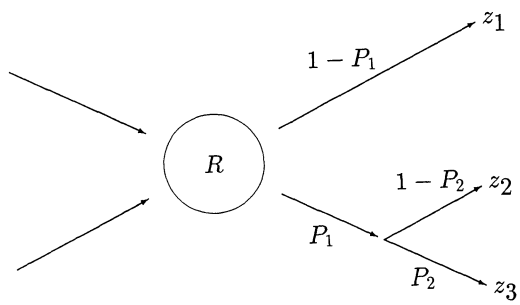

FIG. 9. A functional architecture based on acquisition and allocation leading to three measured phenotypes.

affecting acquisition and allocation of resources. If the number of loci involved in acquiring resources is large enough, relative to those allocating resources, the equilibrium additive genetic covariance may be positive. Another important factor influencing genetic covariance of fitness correlates is the relative strength of selection on acquisition and allocation. If optimal allocation is strongly selected for, as in the upper part of Figure 6, or additional acquisition is weakly selected, as in left part of Figure 7, comparable numbers of allocation and acquisition loci may generate covariances near 0.

The influence of functional architecture adds an ultimate element of uncertainty to the interpretation of genetic covariances. While poor experimental design will lead to estimates of genetic covariances that do not apply to the population of interest (Introduction), it is quite possible that covariances will not match the sign predicted by an optimality model, even at genetic equilibrium. It is not appropriate to assume that all experiments that do not confirm our crude predictions are therefore flawed. Similar conclusions may be drawn from conceptually rather different models that focus on the input of mutational covariance as their primary parameter (Clark, 1987*a*; Charlesworth, 1990), as well as the approach taken by Wagner (1989). The chief advantage of the approach used here is that it provides a framework for the discussion of the importance of mutation in shaping genetic variance-covariance matrices.

The assumption that the pleiotropic effects of each locus are fixed makes functional sense, as genetic effects are expressed through the molecules they code for, and each such molecule will have a limited range of biological effects (cf. Wagner, 1989). Examination of the known phenotypic consequences of mutations at well studied loci (e.g., Lindsley and Grell, 1968) suggests that this view is substantially correct. Barton and Turelli (1989) have argued that the range of pleiotropic effects of each allele at a locus is not so limited. However, the counterexamples cited are primarily of differences in the ranking of effects on phenotypes, of dominance, or of threshold effects (Caspari, 1952; Wright, 1968 pp. 60–63). Neither kind of example argues that pleiotropic effects are so unpredictable that loci could not usefully be categorized. Some developmentally important loci in *Drosophila* produce alleles that affect different sets of phenotypes. In many such cases, molecular analysis shows that such loci consist of regions within which pleiotropic effects are predictable (e.g., Bender et al., 1983). Exceptions exist, such as some of the alleles at the *Notch* locus (Artavanis-Tsakonas, 1988), but they are not common.

A second basic assumption is that loci can be neatly dichotomized into those involved in acquisition and allocation. This is unrealistic in any strict sense, as one can readily imagine, for example, that past allocation

would influence future acquisition, and vice versa. I have chosen to restrict my attention to the simplest case because of its heuristic value, and because there is no empirical guide to which sorts of acquisition-allocation pleiotropy should be added to the model. Selection at loci with pleiotropic effects on acquisition and allocation is straightforward to determine (see Eq. 22 and Appendices), given the character means and phenotypic covariances. Some simple considerations do suggest that acquisition-allocation pleiotropy could either decrease or increase the likelihood of observing positive covariance. For example, if allocation loci are assumed to affect acquisition as well, their allele frequencies would tend to be dominated by the strong selection on acquisition effects, and far less allocation variance would be maintained with pleiotropy than without. Conversely, introducing allocation effects at acquisition loci will change allele frequencies very little, and thus increase allocation variance. In addition, prediction of equilibrium means rapidly becomes unwieldy when there are many patterns of genetic effects. For example, if mutations that increase the amount of resource acquired also directionally affect allocation, mean allocation may be driven far from the selected optimum. This might generate a nonlinear constraint boundary.

While the assumption of no acquisition-allocation pleiotropy may not be realistic, it may be closer to reality than the converse assumption that all loci potentially affect all characters. For example, a holometabolous insect spends its time as a larva acquiring resources that may very largely determine its fitness as an adult. The allocation of those resources to the construction of adult morphology or energy reserves during the pupal period may determine tradeoffs between such characters as fecundity and adult longevity. Since the nature and timing of the metabolic and developmental tasks involved is quite different, it seems reasonable that the loci involved may largely be distinct. On the other hand, comparison of the results of Charlesworth (1990) for parameters that result in similar input of new mutational variance suggest that the conclusions would be the same without the assumption of no acquisition-allocation pleiotropy. The question, in either case, is whether mutations contributing positive covariance are common enough to explain observations of positive covariance among fitness correlates.

In the framework of this model, there clearly must be more acquisition loci than allocation loci before one expects to see positive covariance due to mutation-selection balance at equilibrium. Is it reasonable to expect that there might be 10 or 100 acquisition loci for each allocation locus? I believe such high ratios may sometimes occur. It is first of all clear that very large numbers of loci influence fitness correlates as the genomic mutation rate for such characters is very high (Simmons and Crow, 1977; Crow and Simmons, 1983; Kondrashov, 1988). This makes sense in that every locus in the genome must be capable of affecting fitness, if only by its inactivation. The total gene number in multicellular organisms ranges from about 10^4 for some plants and invertebrates to 10^5 in mammals (Cavalier-Smith, 1985), which leaves room for both substantial numbers of allocation loci and large ratios of acquisition to allocation loci.

Two lines of reasoning suggest that a substantial majority of the loci influencing fitness might cause positive covariance between fitness correlates. First, virtually every aspect of an organism, from behavior to biochemistry may affect the rate that it acquires resources from its environment. On the other hand, it is possible to imagine that allocation takes place through rather simple genetic mechanisms. For example, the hypothetical holometabolous insect discussed earlier has the evolutionary choice of maturing earlier with less resources, or later with more. Allocation loci in this case would be those that control the timing of metamorphosis, such as those influencing juvenile hormone titer. These are probably few in number compared to the behavioral, developmental, and metabolic loci that affect the rate and efficiency of larval feeding.

The second argument springs from the field of metabolic control theory (Kacser and Porteous, 1987; Westerhoff and Kell, 1987; Fell and Sauro, 1985), which seeks to predict the 'flux,' or rate at which a product is produced, through simple biochemical

pathways. In pathways which are closed, with no input or loss of intermediate products, most loci will have only very tiny additive effects on flux, or large recessive ones (Kacser and Burns, 1981; Keightley and Kacser, 1987; Keightley, 1989). This occurs because substrate that is underutilized due to a deleterious mutation at a particular enzymatic step remains in the system. Eventually the increased abundance of the substrate drives the affected reaction forward enough to nearly compensate for the mutation. At most one of the enzyme loci in a linear pathway can have effects on the flux proportional to the allelic effects on enzyme activity. In such a case, all the other loci in that pathway will produce mutants that are completely recessive in their effects on flux (Fell and Sauro, 1985). It seems likely that pathways through which resources are allocated are likely to conform to these assumptions. Therefore, even if many loci are in such pathways, only a small proportion are likely to be capable of producing substantial additive genetic variance in allocation. On the other hand, acquisition is not likely to proceed in closed pathways. For example, there are potentially substantial losses of resource at every step in a predator's handling and absorption of its prey. Inefficiency at each such step would be independent in its effect. Prey that elude capture now will not generally be easier to capture in the future. Nutrients not absorbed during digestion are lost to the organism permanently.

One simple prediction of a mutation-selection balance model of positive correlations is that the correlation of the effects of new mutations on the observed phenotypes should be very near 1. If mutations at each allocation locus increase the variance of $\mathbf{z}$ c times as much as mutation at an acquisition locus, and mean allocation is about 1/2, the correlation due to new mutational variance is

$$\rho_{M\cdot 12} \approx \frac{n_r - cn_p}{n_r + cn_p}. \qquad (34)$$

For n_r/n_p larger than most ZCAs above, such as the 50 to 100 values found when $c = 1$, this correlation will be very large. When positive covariance is found in outbred equilibrium populations, ρ_M provides an indication as to whether the mutation-selection balance model is relevant.

Such experiments have been performed only four times for life-history characters, with mixed results. Mukai and coworkers (Mukai and Yamazaki, 1971; Yoshimaru and Mukai, 1985) estimated the effects on viability and development rate of both homozygous and heterozygous combinations of chromosomes allowed to accumulate mutations without selection for over 50 generations. In both studies, most correlations were greater then 0.9, with a few as low as 0.7. Yoshimaru and Mukai also found the additive correlation in a natural population to be positive, and not significantly different from 0. The functional architecture of this pair of characters may in fact be large enough to explain this near 0 covariance. On the other hand, Simmons et al. (1980), also working with *D. melanogaster* chromosomes, found that new mutants were not correlated in their pleiotropic effects on viability and a measure of fitness including only viability and male mating success. These results are questionable because the estimated variances of viability are inconsistent with the relative times that different sets of chromosomes are allowed to accumulate mutations. Chromosomes from cage populations caused negative correlations between the two phenotypes. It is possible that the difference between these and Mukai's experiments reflects differences in functional architecture of the pairs of traits studied. Lynch (1985) estimated genetic correlations for life-history traits among eight lines of *Daphnia* allowed to accumulate mutations for 50 generations. Almost all the genetic correlations that were significantly different from 0 were very large, often exceeding 1. However, for one phenotype, age at first reproduction, the expected sign of the correlation is reversed, and it also showed a few large positive correlations. More experiments of this type are clearly called for.

A second method for investigating the relevance of the architectural approach to genetic covariance is to attempt to directly measure the fundamental variables acquisition and allocation. In favorable material, a limiting resource might be identified and

studied in addition to the final phenotypes. For example, in a plant, carbon resources acquired and their ultimate use could be assessed. The relative influence of mutation and selection in shaping covariance might then be more amenable to direct study.

I have assumed that genetic variance is maintained by mutation-selection balance, but it may not be an adequate explanation for quantitative genetic variation in all cases (Mukai, 1988; Turelli, 1988; Barton and Turelli, 1989; Barton, 1990). Other nonexclusive hypotheses that could explain that maintenance of genetic variance are balancing selection, genotype-environment interactions, and migration-selection balance. Some attention has recently been focussed on marginal overdominance as a variance maintaining force (Rose, 1982, 1985; Gillespie, 1984; Takano et al., 1987; Gillespie and Turelli, 1989). Particularly appealing in the context of life history theory is Rose's (1982, 1985) application of classical marginal overdominance to loci analogous to allocation loci in the present model. Such polymorphisms could easily maintain large amounts of negative covariance between fitness correlates. However, the data do not suggest that large negative genetic correlations are particularly common (Introduction). The kinds of interactions that Rose suggest are only one of many ways in which balancing selection can occur. Two others are genotype-environment interactions (Takano et al., 1987; Gillespie and Turelli, 1989) and frequency dependent selection (Asmussen and Basnayake, 1990). Both sorts of balancing selection would be as likely to arise in acquisition as in allocation loci, or perhaps more likely, as acquisition processes interact with the external environment. Balancing selection would tend to make covariances unpredictable, as it can generate very large genetic variances at only a few loci. The applicability of balancing selection models in general is questionable, as prodigious efforts to demonstrate its existence have yielded embarassingly few demonstrable examples at specific loci (Lewontin, 1974; Simmons and Crow, 1977; Mukai et al., 1982; Jinks, 1983; Houle, 1989).

A less extreme form of the argument used by Gillespie and Turelli (1989) shows that genotype-environment interactions may help to maintain genetic variance even if they are not large enough to lead to balancing selection. These interactions can be temporal, or spatial. In the latter case, migration may supply substantial genetic variance to local populations (Bulmer, 1980). In this case, as in many models of balancing selection, these processes would be as likely to operate on acquisition loci as allocation loci, and would not necessarily tend to favor a particular covariance pattern. Similarly, environmental changes may lead to bouts of directional selection that will tend to increase genetic variance at either sort of locus. While competing models for the maintenance of genetic variance may have complex effects on covariance, there is no a priori reason to suggest that they should increase the likelihood of observing negative covariance between fitness correlates.

Comparisons among closely related populations suggest that they have evolved differences consistent with the existence of tradeoffs between life-history characters (Reznick, 1985; Partridge and Harvey, 1988). Such evolution takes place readily in my model when the optimal allocation ratio changes. In fact, since I assume that acquisition and allocation are genetically uncorrelated, the sign of the genetic correlation between the observed characters does not affect the response to selection on allocation or acquisition at all. This is an extreme example of the fact that populations will not be prevented from achieving new selective optima unless **G** takes an extreme form (Via and Lande, 1985; Zeng, 1988, 1989). However, acquisition is also free to evolve when the optimal way to acquire resources changes, which would tend to generate positive covariance among populations. Clearly negative covariances are not a necessary consequence of life-history constraints and tradeoffs, either within or among populations.

This reasoning also applies to other kinds of evolutionary constraints and tradeoffs. Long-term constraints come about when no new genetic variation arises with beneficial effects on fitness, and does not require a lack of genetic variance. The existence of tradeoffs strictly requires only the existence of a few loci capable of generating them, and not

that such loci dominate **G**. While genetic variance-covariance matrices are certainly shaped by selection, they also reflect underlying functional architecture. Their relative influence can best be addressed by studying functional architecture itself.

At present, one crude probe of functional architecture that is widely available is the covariance of new mutants as outlined above, and their effects on character means. In the long term, analyses of the functions and relationships of loci that influence quantitative characters may provide us a picture of the functional architecture of well-studied organisms. One advantage of an architectural approach to quantitative genetics is that functional architecture is likely to evolve very slowly. The functional architectures of model organisms such as *Arabidopsis, Mus* and *Drosophila,* are likely to be typical of their taxonomic groups, while the sorts of selection pressures even closely related species currently experience may be extremely different.

Acknowledgments

I thank Z.-B. Zeng, B. Charlesworth, C. C. Cockerham, W. F. Eanes, D. J. Futuyma, S. A. Foster, and two reviewers for their comments on earlier versions of the manuscript. J. Umland and C. Basten helped with the figures. The ideas expressed here benefited from discussion with others too numerous to list. Thanks to you all. This work was supported by NIH grant GM 11546 from the National Institute of General Medicine Sciences, and by NSF grants BSR-8402967 and BSR-8500461 to W. F. Eanes.

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APPENDIX A

In this Appendix, I derive the mean fitness of a genotype i with effects r_i and p_i when the fitness function is

$$W(R, P) = R \exp\left[\frac{-(P - P_o)^2}{2w^2}\right]. \tag{A1}$$

I assume that $F(R, P)$ is bivariate normal, with phenotypic correlation ρ_i. Then

$$\bar{W}_i = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \frac{(R + r_i)\exp\left[\frac{-(P + p_i - P_o)^2}{2w^2}\right]}{\left(2\pi\sqrt{T_R T_P(1 - \rho_i^2)}\right)} \exp\left[\frac{-\left(\frac{(R - \bar{R})^2}{T_R^2} + \frac{(P - \bar{P})^2}{T_P^2} - 2\rho_i\frac{(R - \bar{R})(P - \bar{P})}{T_R T_P}\right)}{\left(2(1 - \rho_i^2)\right)}\right] dR\,dP, \tag{A2}$$

$$= \int_{-\infty}^{\infty} \frac{\exp[-\eta]}{\left(2\pi\sqrt{T_R T_P(1 - \rho_i^2)}\right)} \int_{-\infty}^{\infty} (R + r_i)\exp\left[\frac{-\left(R - (\bar{R} + \Phi(p - \bar{P}))\right)^2}{\left(2(1 - \rho_i^2)\right)}\right] dR\,dP, \tag{A3}$$

where

$$\Phi = \frac{T_{RP}}{T_P},$$

and

$$\eta = \frac{(P + p_i - P_o)^2}{2w^2} + \frac{(P - \bar{P})^2}{2T_P}.$$

Then

$$\bar{W}_i = \int_{-\infty}^{\infty} \frac{\left(\bar{R} + r_i + \Phi(P - \bar{P})\right)}{(\sqrt{2\pi T_P})} \exp[-\eta]\, dP, \tag{A4}$$

Terms of η in P can be collected

$$\eta = \frac{(\bar{P} + p_i - P_o)^2}{2V_s} + \frac{\left(P - \frac{(P_o - p_i)T_P + \bar{P}w^2}{V_s}\right)^2}{2T_P w^2/V_s},$$

where $V_s = T_P + w^2$. Plugging η into Equation A4, and integrating,

$$\bar{W}_i = \exp\left[\frac{-(\bar{P} + p_i - P_o)^2}{2V_s}\right] \sqrt{\frac{w^2}{V_s}} \left(\bar{R} + r_i + \Phi\left(\frac{(P_o - p_i)T_p + \bar{P}w^2}{V_s} - \bar{P}\right)\right) \tag{A5}$$

$$\doteq \exp\left[\frac{-(\bar{P} + p_i - P_o)^2}{2V_s}\right] \sqrt{\frac{w^2}{V_s}} \left(\bar{R} + r_i + T_{RP}\left(\frac{P_o - (\bar{P} + p_i)}{V_s}\right)\right). \tag{A6}$$

Appendix B

In this Appendix, I derive the mean fitness of a genotype i when the fitness function is

$$W(R, P) = R^2(P - P^2). \tag{A7}$$

As in Appendix A, I assume that $F(R, P)$ is bivariate normal, with phenotypic correlation ρ_i, Then,

$$\bar{W}_i = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} (R + r_i)^2(P + p_i - (P + p_i)^2)F(R, P)\, dRdP \tag{A8}$$

$$= \int_{-\infty}^{\infty} F(P)\Big(P + p_i - (P + p_i)^2\Big)\Big(T_R(1 - \rho_i^2) + \Big(\bar{R} + \Phi(P - \bar{P})\Big)^2 + r_i^2$$

$$+ 2r_i(\bar{R} + \Phi(P - \bar{P}))\Big)\, dP \tag{A9}$$

$$= \int_{-\infty}^{\infty} F(P)\Big(P^4(-\Phi^2) + P^3(\Phi^2(1 - 2p_i) - \beta) + P^2\Big((1 - 2p_i)\beta - \alpha + p_i(1 - p_i)\Phi^2\Big)$$

$$+ P\Big((1 - 2p_i)\alpha + p_i(1 - p_i)\beta\Big) + p_i(1 - p_i)\alpha\Big)\, dP, \tag{A10}$$

where

$$\alpha = (\bar{R} + r_i)^2 + T_R - T_{RP}\Phi + \Phi\bar{P}(\Phi\bar{P} - 2(\bar{R} + r_i)),$$

and

$$\beta = 2\Phi((\bar{R} + r_i) - \Phi\bar{P}).$$

Integrating gives the first four noncentral moments of P, and

$$\bar{W}_i = (3T_P^2 + 6T_P\bar{P}^2 + \bar{P}^4)(-\Phi^2) + (3\bar{P}T_P + \bar{P}^3)(\Phi^2(1 - 2p_i) - \beta)$$
$$+ (T_P + \bar{P}^2)((1 - 2p_i)\beta - \alpha + p_i(1 - p_i)\Phi^2) + \bar{P}((1 - 2p_i)\alpha + p_i(1 - p_i)\beta) + p_i(1 - p_i)\alpha. \tag{A11}$$

Finally, this simplifies to

$$\bar{W}_i = ((\bar{R} + r_i)^2 + T_R)(\bar{P} + p_i - (\bar{P} + p_i)^2 - T_P) + T_{RP}(2(\bar{R} + r_i)(1 - 2(\bar{P} + p_i)) - T_{RP}). \tag{A12}$$

Appendix C

For a genotype i, with effects r_i and p_i, the Taylor approximation to third degree of equation (28) is

$$\bar{W}_i \approx \bar{R}^l\bar{P}^k(1 - \bar{P})^j\Big(1 + r_i\Gamma_1 + p_i\Delta_1 + (r_i^2 + T_R)\frac{\Gamma_2}{2} + (r_ip_i + T_{RP})\Delta_1\Gamma_1 + (p_i^2 + T_P)\frac{\Delta_2}{2}$$

$$+ (r_i^3 + 3r_iT_R)\frac{\Gamma_3}{6} + (p_iT_R + 2r_iT_{RP})\frac{\Delta_1\Gamma_2}{2} + (r_iT_P + 2p_iT_{RP})\frac{\Delta_2\Gamma_1}{2} + (p_i^3 + 3p_iT_P)\frac{\Delta_3}{6}\Big), \tag{A13}$$

where $l = j + k$, and

$$\Gamma_f = \frac{l!}{(l - f)!\bar{R}^f},$$

$$\Delta_h = \left(\sum_{g=0}^{h} (-1)^g \frac{j!}{(j-g)!} \frac{k!}{(k-h+g)!} \frac{h!}{g!(h-g)!} \bar{P}^g (1-\bar{P})^{h-g} \right) \left(\bar{P}^h (1-\bar{P})^h \right)^{-1}.$$

This approximation can only be simplified if further restrictions are imposed on j and k.