

# Nonlinear Developmental Processes as Sources of Dominance

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## ABSTRACT

Phenotypes are the products of developmental processes whose dynamics are controlled by genes. In many developmental processes there is a nonlinear relationship between genetic variation and phenotypic variation. These nonlinear relationships can result in the emergence of dominance among alleles that control the developmental process. We explore the properties of dominance relationships in a simple developmental system consisting of a diffusion-gradient-threshold mechanism commonly deployed in pattern formation. We show that a single nonlinear process (diffusion) within this integrated mechanism leads to the emergence of dominance in all components of the mechanism. Unlike the situation in metabolic pathways, where new mutations are most likely to be recessive, the structure of the nonlinearities in this developmental mechanism is such that in certain circumstances new mutations are equally likely to be dominant or recessive. Although the dominance we observe in this system is the result of a physiological process, we also find that dominance can evolve by microevolutionary mechanisms and thus are able to reconcile the opposing views of Fisher and Wright on dominance.

**D**OMINANCE is defined as nonadditive allelic effects at a genetic locus on a phenotypic trait (FALCONER 1981; LYNCH and WALSH 1998). FISHER (1928) viewed dominance as a trait unto itself and showed how the evolution of alleles at modifier genes could transform a selectively advantageous, but recessive, target allele into an allele with a dominant effect. Fisher's proposal for the evolution of dominance was criticized by HALDANE (1930, 1939) and WRIGHT (1929a,b, 1934), because it appeared to require unrealistically large populations and long amounts of time (PROVINE 1971). WRIGHT (1934), by contrast, argued that dominance was not a trait *per se* but instead the result of physiological processes embedded within the development of an organism. Illustrating this argument, WRIGHT (1934) pointed out that the relationship between metabolic flux and the concentration of a single enzyme within an enzymatic pathway should be hyperbolic, with an asymptotic approach to an upper limit. He suggested that it is this nonlinear relationship, rather than direct selection for dominance, that ultimately gives rise to the dominance of alleles.

Fisher's argument for the evolution of dominance through the evolution of modifier genes has since been reformulated (BÜRGER 1983a,b,c; WAGNER and BÜRGER 1985) and shown to be a plausible mechanism for the evolution of dominant gene effects that appears to be consistent with a substantial body of experimental data (MAYO and REINHARD 1997). Wright's idea, based on metabolic flux, is nevertheless the most commonly pre-

sented explanation for the phenomenon of dominance (*e.g.*, see HARTL and CLARK 1989; LYNCH and WALSH 1998).

The general acceptance of Wright's argument is due to a seminal article by KACSER and BURNS (1981) who used enzymatic pathways to explore Wright's argument in a more rigorous manner. Their work showed that "... the recessivity of mutants is an inevitable consequence of kinetic properties of enzyme-catalyzed pathways and that no other explanation is required" (KACSER and BURNS 1981). However, although enzyme-catalyzed pathways are a common component of biological systems not every aspect of a biological system can be described using enzymatic pathways. Furthermore, even within the realm of enzymatic systems Kacser and Burns's predictions do not always hold (BOURGUET and RAYMOND 1998).

Insofar as dominance is the result of nonadditive effects of alleles within a locus, it would seem that any mechanism in which there is a nonlinear relationship between allele activity and phenotypic value will, by definition, exhibit dominance. Nonetheless, in spite of recent suggestions to the contrary (*e.g.*, PORTEOUS 1996), enzyme-catalyzed pathways are not the only, nor even necessarily the most common, physiological sources of dominance. Indeed, OMHOLT *et al.* (2000) have recently shown that dominance is also an emergent property of genetic regulatory networks that contain positive or negative feedback.

Here we argue that emergent dominance is not restricted to metabolic pathways with constitutive enzymes or to regulatory genetic circuits but that it is a general property of any mechanism that generates a nonlinear relationship between genetic value and phenotypic value.

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Most regulatory mechanisms in development and physiology involve nonlinear processes such as negative and positive feedback, cooperativity, inhibition, or the diffusion of a signal. Because gene products typically mediate such regulatory processes, one would expect a nonlinear relationship between genetic and phenotypic variation in the products of those processes. Below we explore the consequences of nonlinearity through a detailed analysis of a simple developmental mechanism in which the value of a trait is determined by a morphogen diffusion gradient and threshold. NIJHOUT and PAULSEN (1997) used the same mechanism to generate a one-dimensional pattern and examined the consequences of genetic variation and phenotypic selection on the genetic response to selection. In this analysis we extend this previous study by exploring how specific forms of nonlinearity lead to different manifestations of dominance. We show that dominance is not a static property of a particular genetic or developmental mechanism but is sensitive to allelic variation and should, therefore, be subject to microevolutionary change.

#### METHODS

**Developmental model:** We assume that the phenotypic trait value is controlled by a simple diffusion gradient-threshold mechanism (NIJHOUT and PAULSEN 1997). Such gradient-threshold mechanisms are widespread in early embryonic development and constitute what are arguably the simplest regulatory mechanisms in development (MEINHARDT 1982; HELD 1992). Gradient molecules are often transcription factors that control thresholded gene expression and include such well-studied factors as *bicoid*, *hunchback*, *nanos*, *decapentaplegic*, *wingless*, *caudal*, *hedgehog*, and *distalless* (e.g., KALTHOFF 1995).

For purposes of illustration we assume that a morphogen, such as a transcription factor or receptor ligand, is produced at a point source where it is maintained at a fixed concentration,  $S$ . The morphogen diffuses from this point source with a diffusion coefficient  $D$ . As it diffuses the morphogen decays at a fixed rate  $\rho$ . This process leads to the formation of a morphogen gradient that evolves over time toward a stable equilibrium state. The equation governing the dynamics of morphogen concentration  $y$  over time  $t$  and space  $x$  is

$$\frac{\partial y}{\partial t} = D \frac{\partial^2 y}{\partial x^2} - \rho y. \quad (1)$$

The trait value is determined by the location at which the concentration of the morphogen  $y$  drops below a threshold value  $T$  at some time  $t$ . For simplicity, we assume that the diffusion gradient has closely approached its equilibrium state at the time the trait value is determined. The equilibrium assumption allows us

to ignore the time component of Equation 1, leaving us with the ordinary differential equation

$$D \frac{d^2 y}{dx^2} - \rho y(x) = 0. \quad (2)$$

We define our coordinate system such that the source of the morphogen is located at  $x = 0$  and we assume that  $x$  is unbounded. On the basis of these assumptions, we set  $y(0) = S$  and  $y(\infty) = 0$  as the boundary conditions. This gives us the unique solution to Equation 2,

$$y(x) = S \exp\left[-\sqrt{\frac{\rho}{D}}x\right], \quad (3)$$

where the concentration of the morphogen  $y$  is a function of distance from the source  $x$ . The phenotypic trait value  $P$  is determined by the location at which the concentration gradient crosses the threshold value  $T$ . That is,  $P = x_T$  where  $x_T$  satisfies the condition  $y(x_T) = T$ . On the basis of Equation 3 we can solve for  $P$  to get

$$P = \begin{cases} \sqrt{\frac{D}{\rho}} \ln\left(\frac{S}{T}\right) & \text{if } S > T, \\ 0 & \text{else.} \end{cases} \quad (4)$$

The form of Equation 4 indicates that the trait value  $P$  is dependent on the two ratios  $S/T$  and  $D/\rho$  (Figure 1). Because the phenotypic trait is, in part, dependent on the ratio of the parameters, there is an essentially infinite number of combinations of  $\rho$  and  $D$  or  $S$  and  $T$  that will give rise to the same phenotypic trait value.

From Equation 4 it is clear that the relationship between each parameter and trait value is nonlinear (Figure 2). For the decay parameter, trait value  $P$  is a concave monotonic decreasing function of  $\rho$ . In contrast, for the diffusion parameter,  $P$  is a convex monotonic increasing function of  $D$ . Both the source and threshold parameters are stepwise functions with regions in which the trait value is zero. For the source gene this region is  $(0, T)$ , after which  $P$  is a convex monotonically increasing function of  $S$ . For the threshold gene this region is  $(S, \infty)$ , before which  $P$  is a concave monotonically decreasing function of  $T$ .

**Linking phenotype to genotype:** To link the behavior of our developmental model to the genotype of a diploid individual, we assume that all of the model's parameters ( $S$ ,  $T$ ,  $D$ , and  $\rho$ ) are genetically determined. Although each parameter is itself likely to be polygenic, we assume that variation in each parameter is affected primarily by variation at one of those gene loci. For instance, a gene that affects the diffusion coefficient of a ligand could do so by affecting the number of gap junctions between cells, or the ionic properties of those junctions or, for an extracellular signal, the properties of the extracellular matrix. Genes that affect the synthesis or catabolism of a ligand are obvious. A gene that affects the value of a threshold could do so by affecting the number of receptors available for the ligand or the

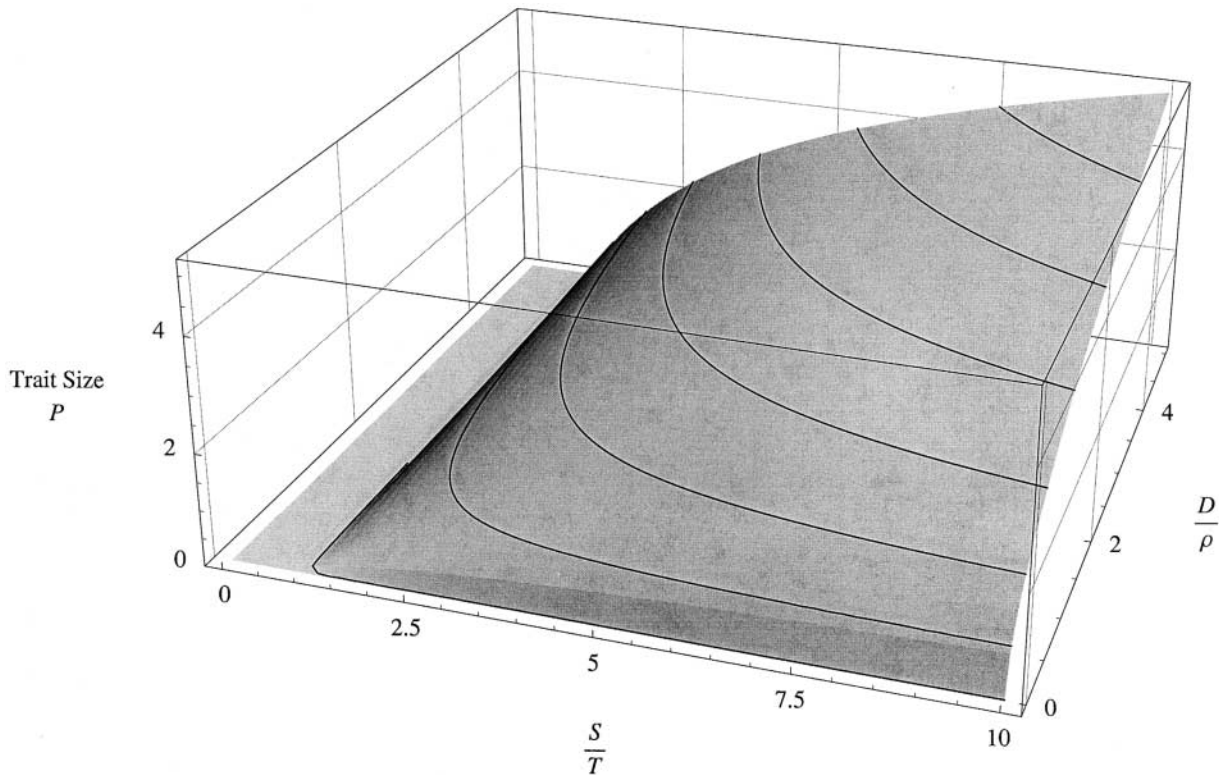


FIGURE 1.—Trait value  $P$  as a function of the ratios  $D/\rho$  and  $S/T$ . Flat region where  $S/T < 1$  corresponds to values at which the morphogen concentration  $y(x)$  never gets above the threshold value  $T$ . Once  $S/T > 1$ ,  $P$  increases monotonically and without bound with both ratios. Thus, as  $D$  or  $S$  go to  $\infty$  or  $\rho$  or  $T$  go to 0,  $P$  goes to infinity.

equilibrium constant of ligand-receptor binding. Finally, we assume that each gene segregates independently of all the other genes that affect phenotypic variation in this system.

For the rest of this section and in the following one, we use the symbol  $L$  as a general notation for any one of the four genes (*i.e.*,  $L \in \{S, T, D, \rho\}$ ). Each allele at a given gene produces a gene product that has a particular activity level (*i.e.*, allelic activity). The model parameter values are determined by the mean activity value of the two alleles for each of the four genes. For consistency, when discussing two different alleles we always label the allele with the lower activity level as  $L_1$  and the allele with the higher activity level  $L_2$ . We identify the different genotypes by using the gene symbol whose dominance term we are measuring and a double subscript, one for each allele. Thus,  $L_{11}$  and  $L_{22}$  would represent the activity levels of the  $L_1$  and  $L_2$  homozygotes, respectively, while  $L_{12}$  would represent the activity level of heterozygote genotype.

**Calculating dominance:** Operationally, dominance is a measure of the deviation of the heterozygote's observed trait value from its expected value based on the phenotype of the two homozygotes. Because  $P$  is a non-linear function of each of the four genes, we expect to find dominance effects for each of these genes. Thus, when measuring dominance at any one gene, we assume

that the two parent genotypes are homozygous for the same alleles at the genes controlling the other parameters.

Using Equation 4 we can determine the trait value of both homozygous individuals. In the absence of dominance, the expected trait value of the heterozygote  $L_{12}$  is the mean of the trait value of the two homozygotes,  $L_{11}$  and  $L_{22}$ . To make our analysis scale-independent, we define dominance explicitly as the relative deviation of the heterozygote from its expected value. Consequently, we divide the absolute deviation by the expected heterozygote value.

Thus for any given gene  $L$  the dominance value  $\delta_L$  is defined as

$$\delta_L = \frac{P(L_{12}) - (1/2)(P(L_{22}) + P(L_{11}))}{(1/2)(P(L_{22}) + P(L_{11}))}. \quad (5)$$

A negative  $\delta_L$  value indicates that the heterozygote trait value is less than expected, and a positive value indicates that the heterozygote trait value is greater than expected. Because the sign of the slope between trait value and allele activity ( $dP/dL$ ) is not consistent across all genes, the sign of  $\delta_L$  does not reliably indicate which homozygous genotype the heterozygote most closely resembles. Instead the sign simply indicates whether or not the heterozygote is above or below its expected value. Because the trait value always changes in a mono-

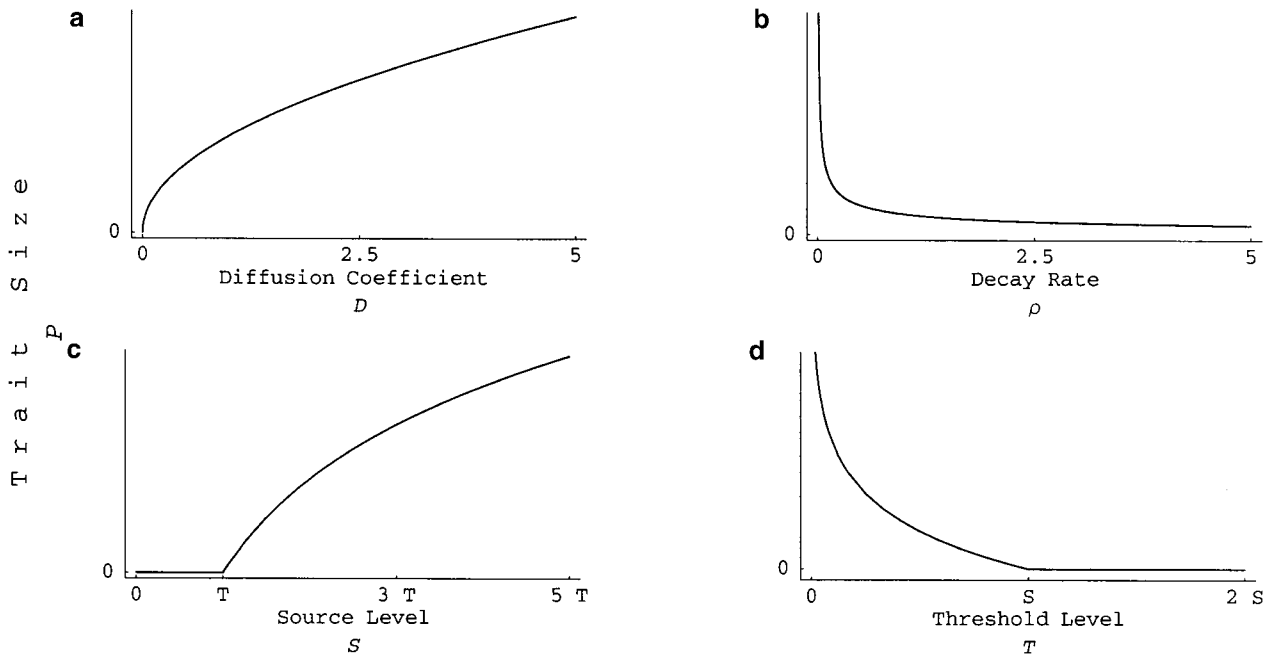


FIGURE 2.—Trait value  $P$  as a function of each model parameter. A concave relationship between a parameter and trait value should lead to a positive dominance term, and a convex relationship should lead to a negative dominance term. (a) Diffusion coefficient,  $D$ ; (b) decay rate,  $\rho$ ; (c) source concentration,  $S$ ; (d) threshold level,  $T$ .

tonic manner with the activity for a given parameter, the heterozygote trait value will always be bounded by the two homozygotes. Therefore,  $\delta_L$  will always be bounded by  $-1$  and  $1$ .

Analysis of Equation 5 indicates that dominance is scaled by the relative difference in the activity of the two alleles rather than their absolute values. As a result we use the following notation for representing the activity level of the two alleles relative to their mean value  $\bar{L}$ . If  $\Delta L$  is the amount by which two alleles' activities deviate from their mean value, then  $L_1$  has an activity level of  $\bar{L} - \Delta L$  and  $L_2$  has an activity level of  $\bar{L} + \Delta L$ . The relative difference in activity of two alleles is, therefore,  $\Delta L/\bar{L}$ , which varies from 0 to 1. When  $\Delta L/\bar{L} = 0$ , the activities of the two alleles are identical. When  $\Delta L = 1$ , the activity of  $L_1$  is  $\bar{L} - \Delta L = 0$  and the activity of  $L_2$  is  $\bar{L} + \Delta L = 2\bar{L} > 0$ . Using Equation 5, we derive the dominance term for each gene. The results are summarized in Table 1 and plotted in Figures 3–6.

## RESULTS

The degree of dominance is small when the differences between the activity of the two alleles are small (*i.e.*,  $\Delta L/\bar{L} \approx 0$ ) for all four genes. This reflects the fact that, although the relationship between allele activity and trait is nonlinear, over short distances a linear approximation of the curve provides a reasonable fit. As the difference between the two alleles' activity increases, the curvature of the genotype-phenotype map illustrated in Figure 1 becomes more pronounced.

If  $\bar{S}/\bar{T} < 1$ , then  $\delta_\rho$  and  $\delta_D$  are undefined for the  $D$  and  $\rho$  genes because none of the genotypes will express the trait. The terms  $\delta_S$  and  $\delta_T$  likewise are undefined in regions where none of the genotypes express the trait although the conditions under which this occurs are somewhat more complex (see below).

**Diffusion coefficient:** Whenever  $\bar{S}/\bar{T} > 1$ , the dominance effect at the diffusion coefficient gene,  $\delta_D$ , is independent of the other genes. Because of the convex relationship between  $P$  and  $D$ , the midpoint of a line drawn between any two points on the phenotype-genotype curve (Figure 2a) will be below this curve. As a result the sign of dominance at the diffusion gene is always positive (Figure 3). Even at the most extreme  $\Delta D/\bar{D}$  value of 1, the heterozygote has an intermediate form corresponding to a dominance value of  $\sqrt{2} - 1$ . Thus we never expect to find complete dominance at the diffusion coefficient gene. Because the allele with the larger activity level  $D_2$  will always have a dominant effect on the trait, mutations that decrease  $D$  will be recessive to the wild-type allele. Conversely, mutations that increase  $D$  will be dominant to the wild-type allele.

**Morphogen decay:** As with the diffusion coefficient, whenever  $\bar{S}/\bar{T} > 1$ , the dominance effect at the morphogen decay gene,  $\delta_\rho$ , is independent of the other three genes. Because of the concave relationship between  $P$  and  $\rho$ , the midpoint of a line drawn between any two points on the phenotype-genotype curve (Figure 2b) will be above this curve. As a result the sign of dominance at the decay gene is always negative (Figure 4). In the extreme case where  $\Delta\rho/\bar{\rho} = 1$ ,  $\rho_1$  is equal to

TABLE 1

Solutions for dominance terms,  $\delta_i$ , for all four genes ( $D$ ,  $\rho$ ,  $S$ ,  $T$ ) under all possible conditions

Term	Conditions	Nonzero genotypes
$\delta_D = \begin{cases} \frac{2}{\sqrt{1 - \Delta D/\bar{D}} + \sqrt{1 + \Delta D/\bar{D}}} - 1 \\ \text{Undefined} \end{cases}$	$\bar{S} > \bar{T}$	All
	$\bar{S} \leq \bar{T}$	None
$\delta_\rho = \begin{cases} \frac{2}{\sqrt{\frac{1}{1 - \Delta\rho/\bar{\rho}}} + \sqrt{\frac{1}{1 + \Delta\rho/\bar{\rho}}}} - 1 \\ \text{Undefined} \end{cases}$	$\bar{S} > \bar{T}$	All
	$\bar{S} \leq \bar{T}$	None
$\delta_S = \begin{cases} -\frac{\ln(1 - (\Delta S/\bar{S})^2)}{\ln(1 - (\Delta S/\bar{S})^2) + 2 \ln(\bar{S}/\bar{T})} \\ \frac{\ln(\bar{S}/\bar{T}) - \ln(1 + (\Delta S/\bar{S})^2)}{\ln(\bar{S}/\bar{T}) + \ln(1 + (\Delta S/\bar{S})^2)} \\ -1 \\ \text{Undefined} \end{cases}$	$\bar{T} < \bar{S} - \Delta S$	$S_{11}, S_{12}, S_{22}$
	$\bar{S} - \Delta S \leq \bar{T} < \bar{S}$	$S_{12}, S_{22}$
	$\bar{S} \leq \bar{T} < \bar{S} + \Delta S$	$S_{22}$
	$\bar{S} + \Delta S \leq \bar{T}$	None
$\delta_T = \begin{cases} \frac{\ln(1 - (\Delta T/\bar{T})^2)}{2 \ln(\bar{S}/\bar{T}) - \ln(1 - (\Delta T/\bar{T})^2)} \\ \frac{\ln(\bar{S}/\bar{T}) + \ln(1 + (\Delta T/\bar{T})^2)}{\ln(\bar{S}/\bar{T}) - \ln(1 + (\Delta T/\bar{T})^2)} \\ -1 \\ \text{Undefined} \end{cases}$	$\bar{T} + \Delta T < \bar{S}$	$T_{11}, T_{12}, T_{22}$
	$\bar{T} \leq \bar{S} < \bar{T} + \Delta T$	$T_{11}, T_{12}$
	$\bar{T} - \Delta T \leq \bar{S} < \bar{T}$	$T_{11}$
	$\bar{S} \leq \bar{T} - \Delta T$	None

For the diffusion and decay genes,  $D$  and  $\rho$ , respectively, dominance is undefined whenever  $\bar{S} < \bar{T}$  because under these conditions none of the genotypes will express the trait. For the source and threshold genes,  $S$  and  $T$ , respectively, the situation is more complex, but again the dominance terms are undefined when all three genotypes fail to express the trait. The other cases correspond to when one, two, or all three genotypes have nonzero trait values.

0 and the morphogen never decays in the  $\rho_{11}$  genotype. For this genotype the equilibrium morphogen concentration,  $y(x)$ , is equal to  $S$  for all  $x$ . Given the previous condition that  $\bar{S}/\bar{T} > 1$  and because  $y(x) = \bar{S} > \bar{T}$  for all  $x$ , then the threshold is never crossed and  $P(\rho_{11}) = \infty$ . In contrast, the trait values of  $\rho_{12}$  and  $\rho_{22}$  are always finite. Thus  $\delta_\rho$  approaches  $-1$  as  $\Delta\rho/\bar{\rho}$  approaches 1. In reality, organism and trait values are always finite and, therefore, complete dominance at this gene can be approached but never achieved. Nonetheless, as with the diffusion gene, the allele with the larger activity

level will always be dominant. Therefore, mutations that decrease  $\rho$  will be recessive to the wild-type allele while, conversely, mutations that increase  $\rho$  will be dominant to the wild-type allele.

The behavior of dominance at the source and threshold levels is far more complex than at the other two loci. This is so because  $\delta_S$  and  $\delta_T$  are not only functions of the relative difference in activity between the alleles at the respective locus but also of the ratio  $\bar{S}/\bar{T}$ . Consequently, we find that there are four distinct regions in genotypic space corresponding to regions where none,

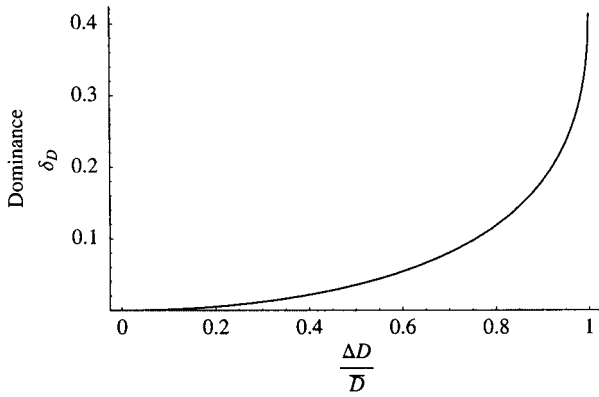


FIGURE 3.—Dominance effects at the diffusion coefficient gene,  $\delta_D$ , as a function of the relative difference between the activity levels of  $D_1$  and  $D_2$ ,  $\Delta D/\bar{D}$ , assuming that  $S/T > 1$ . Dominance at this gene increases with  $\Delta D/\bar{D}$  reaching a maximum value of  $\sqrt{2} - 1$  when  $\Delta D/\bar{D} = 1$ . A positive  $\delta_D$  value indicates that the heterozygote is more similar to the  $D_2$  homozygote than the  $D_1$  homozygote.

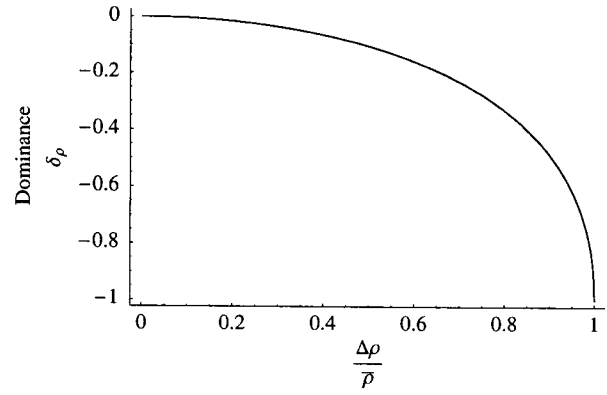


FIGURE 4.—Dominance effects at the morphogen decay gene,  $\delta_\rho$ , as a function of the relative difference between the activity levels of  $\rho_1$  and  $\rho_2$ ,  $\Delta\rho/\bar{\rho}$ , assuming that  $S/T > 1$ . Dominance for this gene is always negative and its absolute strength increases with  $\Delta\rho/\bar{\rho}$ . The fact that  $\delta_\rho$  is 1 at  $\Delta\rho/\bar{\rho} = 1$  is somewhat misleading because this requires the trait value of the  $\rho_{11}$  genotype to be infinite. In reality  $P(\rho_{11}) < \infty$  and thus  $\delta_\rho > -1$ . A negative  $\delta_\rho$  value indicates that the heterozygote is more similar to the  $\rho_2$  homozygote than the  $\rho_1$  homozygote.

one, two, and all three of the genotypes have nonzero trait values. In the text and figures we refer to these as regions 0, 1, 2, and 3, respectively. We forewarn the reader that the detailed descriptions given in the following sections are rather involved due to the complex relationships that define each of the regions. Our goal is to illustrate that, even in a simple developmental system, the dominance effects are strongly dependent on the location of the system in its genotypic space.

**Source level:** For the source gene, the boundary between region 0 and region 1 is defined by the equality  $S + \Delta S = \bar{T}$ . Region 0 corresponds to the blank region in the foreground of Figure 5 where  $\Delta S/\bar{S} < \bar{T}/\bar{S} - 1$ . Consequently, none of the genotypes express the trait and dominance is, therefore, undefined. Region 1 corresponds to the flat region in the foreground of Figure 5 where  $\Delta S/\bar{S} > \bar{T}/\bar{S} - 1$  and  $\bar{S}/\bar{T} < 1$ . Within region 1, as well as regions 2 and 3,  $P(S_{22}) > 0$ , hence the expected value of the heterozygote is also nonzero. However, because in region 1  $\bar{S}/\bar{T} < 1$  and  $P(S_{11}) = P(S_{12}) = 0$ , the dominance value in this region is  $-1$ .

The boundaries of region 2 are  $\bar{S} < \bar{T}$  and  $S - \Delta S > \bar{T}$ . In Figure 5, this corresponds to the region below and to the right of the ridge where  $\bar{S}/\bar{T} > 0$  and  $\Delta S/\bar{S} > 1 - \bar{T}/\bar{S}$ . Within this region, both the  $S_{22}$  homozygote and the  $S_{12}$  heterozygote express the trait but the  $S_{11}$  homozygote does not. Because the logarithmic function is a decelerating one, the difference between  $\ln(X)$  and  $\ln(X/2)$  will decrease toward 0 as  $X$  approaches infinity. Therefore, starting at low  $\bar{S}$  values,  $\delta_S$  increases from  $-1$  and approaches 1 as  $\bar{S}$  increases.

Region 3 is bounded by the inequality  $S - \Delta S > \bar{T}$ . In Figure 5, this corresponds to the area above the ridge where  $\Delta S/\bar{S} \leq 1 - \bar{T}/\bar{S}$ . Because in this region  $S_1 > \bar{T}$ , the genotype-phenotype relationship is essentially concave (Figure 2c). As a result the dominance term in region 3 is always positive and increases with  $\Delta S/\bar{S}$ .

Thus for a given value of  $\bar{S}/\bar{T}$ ,  $\delta_S$  is always greatest at the boundary between regions 2 and 3. The location of this boundary relative to  $\Delta S/\bar{S}$  increases with increasing values of  $\bar{S}/\bar{T}$ . At the limit of  $\bar{S}/\bar{T} \rightarrow \infty$ , the boundary approaches  $\Delta S/\bar{S} = 1$  and  $\delta_S$  approaches 1.

In contrast to the decay and diffusion genes, at the source gene the allele with the higher activity level,  $S_1$ , is neither always dominant nor always recessive. This is so because whether the midpoint of a line drawn between two points in the genotype-phenotype curve (Figure 2c) lies above or below the curve depends on where the points are chosen. For example, imagine  $S_1$  lies on the flat portion of the genotype-phenotype curve, while  $S_2$  lies on the curved portion (*i.e.*,  $S_1 < \bar{T} < S_2$ ). If  $S_2$  is relatively small, then the midpoint of the line connecting the two points  $S_1$  and  $S_2$  will be above the trait value curve and the lower valued allele will have dominant effects. However, if  $S_2$  is relatively large, then the midpoint of our line will be below the trait value curve and thus the higher valued allele will have dominant effects.

The fact that  $\delta_S$  can vary between  $-1$  and 1 implies that the dominance effects can be quite strong. However, the degree and direction of dominance effects depend on the relative difference between  $S_1$  and  $S_2$  and the ratio  $\bar{S}/\bar{T}$ .

**Threshold level:** For the threshold gene, the boundary between region 0 and region 1 is defined by the equality  $T - \Delta T = \bar{S}$ . Region 0 corresponds to the blank region in the foreground in Figure 6 where  $\bar{S}/\bar{T} \leq 1 - \Delta T/\bar{T}$  and, consequently,  $T_{11}$ ,  $T_{12}$ , nor  $T_{22}$  expresses the trait. Region 1 corresponds to the flat region in the foreground of Figure 6 where  $\bar{T}/\bar{S} - 1 < \Delta T/\bar{T}$  and  $\bar{S}/\bar{T} < 1$ . Within region 1, as well as regions 2 and 3,  $P(T_{11}) > 0$ ; hence the expected value of the heterozygote is also nonzero. In region 1  $\bar{S}/\bar{T} < 1$  and  $P(T_{12}) = P(T_{22}) = 0$ , so the dominance value in this region is  $-1$ .

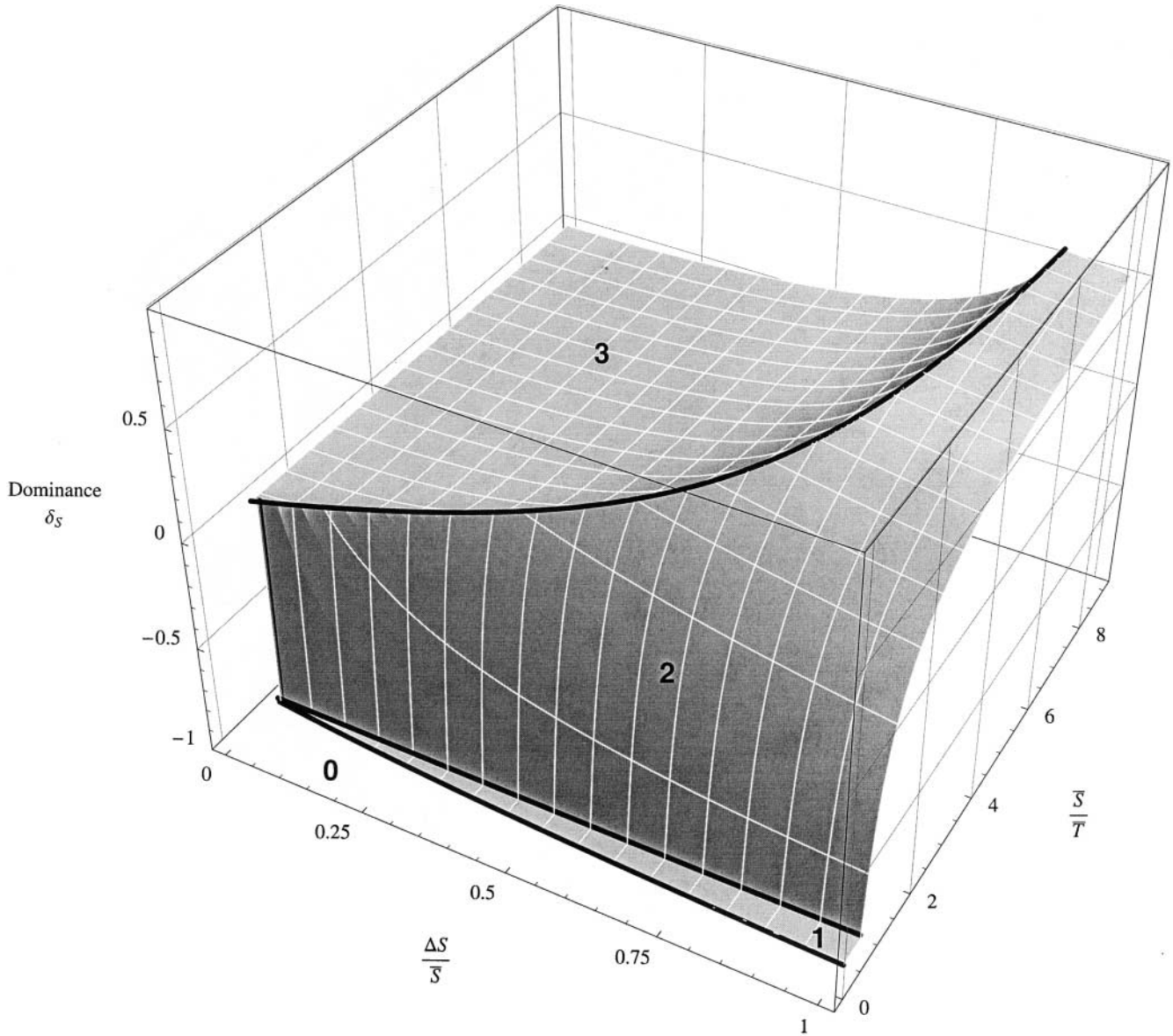


FIGURE 5.—Dominance effects at the morphogen source concentration gene,  $\delta_S$ , as a function of the relative difference between the activity levels of  $S_1$  and  $S_2$ ,  $\Delta S/\bar{S}$ , and  $S/T$ . Black lines and numbers correspond to regions in which zero, one, two, or all three genotypes express the trait. A positive  $\delta_S$  value indicates that the heterozygote is more similar to the  $S_2$  homozygote than the  $S_1$  homozygote.

The boundaries of region 2 are  $\bar{T} < \bar{S}$  and  $\bar{S}/\bar{T} - 1 > \Delta T/\bar{T}$ . Within this region, both the  $T_{11}$  homozygote and the heterozygote  $T_{12}$  express the trait while the  $T_{22}$  does not. If  $\Delta T/\bar{T} < 1$ , then  $\delta_T$  rapidly approaches 0 especially at low values of  $\Delta T/\bar{T}$  as can be seen in Figure 6.

If  $\Delta T/\bar{T} = 1$ , then  $T_1 = 0$ . This implies that  $P(T_{11}) = \infty$  because  $\lim_{x \rightarrow \infty} y(x) = 0$ . Because  $\Delta T/\bar{T} > 0$ , both  $P(T_{12})$  and  $P(T_{22})$  are always finite. Thus,  $P(T_{12})$  is always more similar to  $P(T_{22})$  than  $P(T_{11})$ . Consequently,  $\delta_T$  approaches  $-1$  as  $\Delta T/\bar{T}$  approaches 1. This is similar to the results found with  $\delta_\rho$  as  $\Delta\rho/\bar{\rho}$  approached 1 and is due to the fact that both  $\rho$  and  $T$  are found in the denominators of terms within Equation 4. Unlike the source gene, the transition from region 2 to region 3 occurs seamlessly. As with the decay gene, the concave

relationship between  $P$  and  $T$  ensures that the midpoint of a line drawn between two points on the phenotype-genotype curve (Figure 2d) will be above this curve. Mutations that decrease  $T$  will be recessive to the wild-type allele, whereas mutations that increase  $T$  will be dominant to the wild-type allele.

## DISCUSSION

In the model used by NIJHOUT and PAULSEN (1997), the alleles at each genetic locus acted additively at the physiological level, but dominance emerged due to the nonlinear nature of the developmental process itself. Our article expands on this work by showing analytically that some degree of dominance can be found across

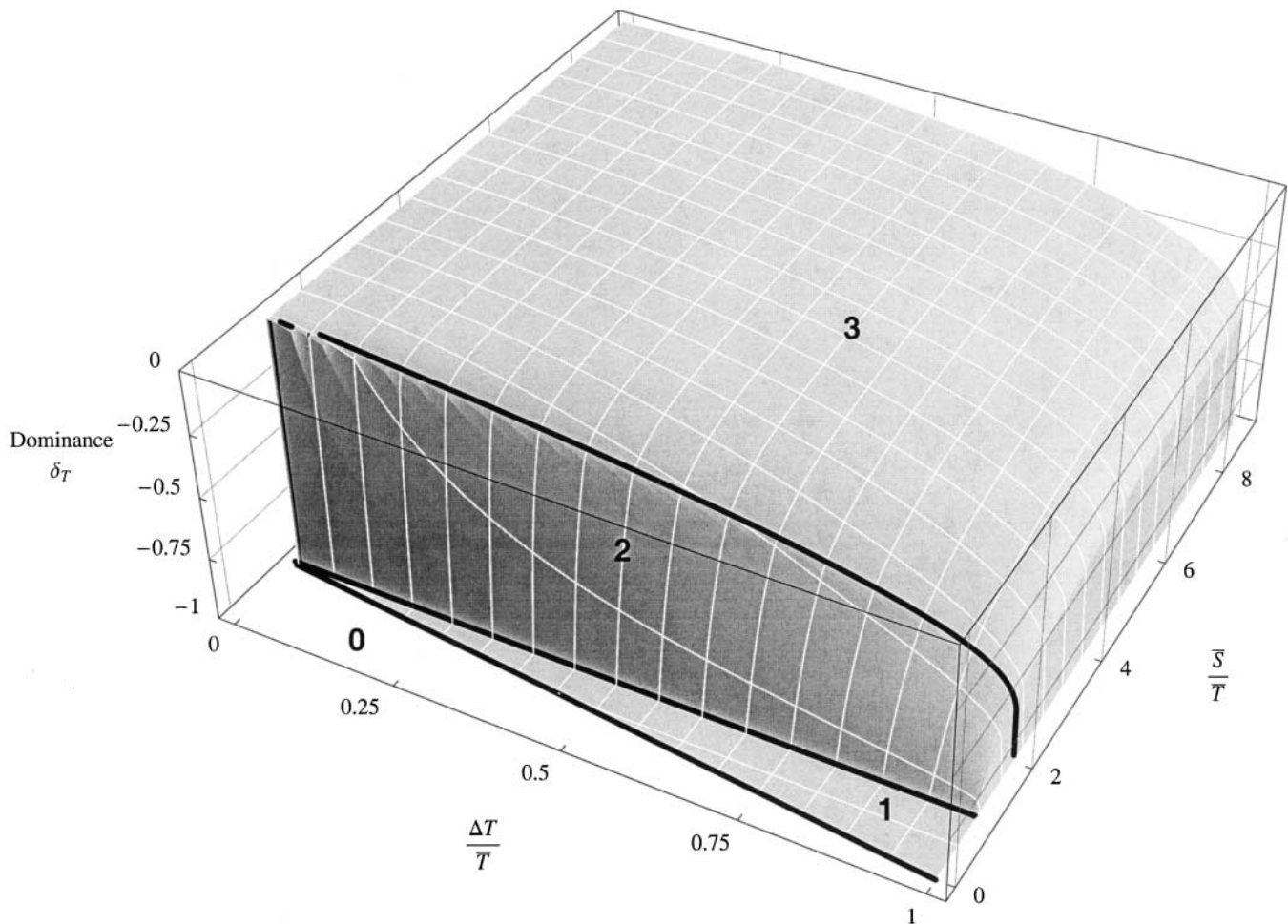


FIGURE 6.—Dominance effects at the threshold gene,  $\delta_T$ , as a function of the relative difference between the activity levels of  $T_1$  and  $T_2$ ,  $\Delta T/\bar{T}$ , and  $S/T$ . Black lines and numbers correspond to regions in which zero, one, two, or all three genotypes express the trait. A negative  $\delta_T$  value indicates that the heterozygote is more similar to the  $T_2$  homozygote than the  $T_1$  homozygote.

virtually all of genotypic space. We emphasize, however, that the developmental system explored here, like the biochemical system of KACSER and BURNS (1981) and the genetic circuits of OMHOLT *et al.* (2001), is a special case that illustrates different aspects of the evolution of dominance. The general principle underlying all of these cases is that they are systems in which the relationship between allelic variation and trait variation is nonlinear. Any nonlinearity in the genotype-phenotype map, irrespective of the mechanism that brings it about, can act as a source of dominance.

To conduct the analysis reported here, we assumed that the trait was formed after the morphogen had reached its equilibrium distribution. Although we do not know whether real developmental systems are in diffusive equilibrium, we suspect that this is seldom the case. However, the nonlinearity of this system should decrease as the equilibrium distribution of the morphogen is approached. Therefore, dominance should be stronger in systems that are far from equilibrium than in those that approach equilibrium. Thus our findings

should represent a lower bound for dominance effects in systems of this kind.

Although the alleles in this diploid system act additively at the “physiological” (*i.e.*, parameter) level, they exhibit dominance at the phenotypic level because of the nonlinearity of the developmental mechanism that translates genetic value into a phenotypic trait value. Our work shows that a single nonlinear process (diffusion, in this case) within an integrated developmental mechanism can induce the emergence of dominance in all the components of that mechanism. We suspect that the nonlinear nature of developmental processes helps to explain the ubiquity of dominance in genes that affect morphological and quantitative traits. These dominant gene effects, however, may be more difficult to detect when each gene has a small effect and, thus, its effect is approximately linear.

The dominant behavior of wild-type alleles in pathways of constitutive enzymes results from the fact that (a) wild-type genetic values are expected to be found on or near the asymptotic region of the genotype-phenotype



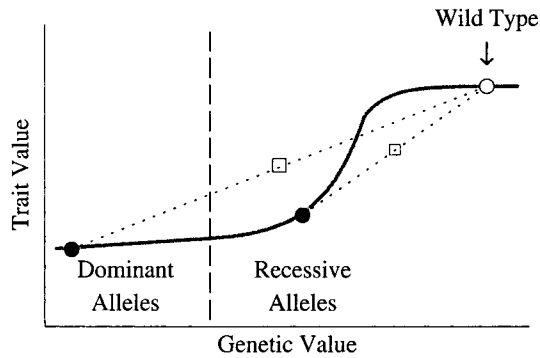


FIGURE 7.—Illustration of how the presence of an inflection point leads to the possibility of either dominant or recessive alleles relative to the wild type. If the wild type is at the location indicated, then alternative alleles (●) with genetic values to the right of the vertical dashed line will be recessive to the wild type because the observed heterozygote trait value will be greater than the expected value (□). Conversely, alleles to the left of the dashed line will be dominant because the observed heterozygote trait value will be less than the expected value.

type curve (WRIGHT 1934; KACSER and BURNS 1981) and (b) mutations appear to be more likely to disrupt, rather than enhance, the catalytic activity of an enzyme, hence making them hypomorphic at the physiological level.

In the developmental mechanism explored here, as in the genetic circuit model of OMHOLT *et al.* (2000), there is no *a priori* reason to expect that a wild-type allele is necessarily at an asymptotic region of the genotype-phenotype curve. Indeed, in this system the relationship between trait value and activity is not always asymptotic (*e.g.*, *S* and *D* genes). Furthermore, it is not clear whether or not we should expect mutations to be hypermorphic or hypomorphic at the physiological level. More importantly, even if there was an *a priori* reason to expect mutations to be hypomorphic, such mutations would not necessarily be recessive. For example, a mutation that alters the amino acid sequence of the morphogen could change its activity. Alternatively, a mutation in the regulatory region of its gene could alter the level of morphogen expression. Because such mutations are more likely to reduce the affinity of the morphogen to its target rather than increase it (or to reduce the level of its expression rather than increase it), one might expect mutations at the source gene to act in a hypomorphic manner by causing a reduction in the effective morphogen source concentration, *S*. However, whether the effect of such a mutation is dominant or recessive depends on the ratio of *S* to *T* for the resident alleles and the difference in activity between the mutant and wild-type alleles. Context-dependent dominance of this type will occur in any system in which the relationship between genetic and phenotypic value has a threshold (Figure 2c) or an inflection point, such as the specific regulatory systems studied by OMHOLT *et al.* (2000). If

in such a system there is a broad range of hypomorphic alleles, it is possible for some of these to be dominant and others to be recessive, depending entirely on their physiological distance from the wild-type allele (Figure 7).

Although dominance is an inherent product of the developmental mechanism, rather than modifier genes as proposed by FISHER (1928), this does not mean that dominance cannot evolve. In this, as in all nonlinear polygenic systems, there are multiple combinations of gene activities that lead to an identical trait value (*e.g.*, contours in Figure 1). Thus any given trait value can be achieved by many different combinations of genetic values that lead to different combinations of dominance potentials for each of the genes. Depending on the distribution of allelic values and the relationship between trait value and fitness, selection could drive a population to a region in which dominance effects are minimized or maximized for a particular gene. Thus dominance at a particular gene can also evolve through the movement of a population along a trait value contour to a new location on the phenotype-genotype surface (RICE 1998). This view of the evolution of dominance is consistent with the suggestion by WRIGHT (1934) and KACSER and BURNS (1981) that dominance results from nonlinearities in the underlying physiology. Interestingly, it is also consistent with a more general interpretation of FISHER (1928) that selection can lead to a change in dominance by changes at other loci.

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