Gene Regulatory Networks Generating the Phenomena of Additivity, Dominance and Epistasis

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ABSTRACT

We show how the phenomena of genetic dominance, overdominance, additivity, and epistasis are generic features of simple diploid gene regulatory networks. These regulatory network models are together sufficiently complex to catch most of the suggested molecular mechanisms responsible for generating dominant mutations. These include reduced gene dosage, expression or protein activity (haploinsufficiency), increased gene dosage, ectopic or temporarily altered mRNA expression, increased or constitutive protein activity, and dominant negative effects. As classical genetics regards the phenomenon of dominance to be generated by intralocus interactions, we have studied two one-locus models, one with a negative autoregulatory feedback loop, and one with a positive autoregulatory feedback loop. To include the phenomena of epistasis and downstream regulatory effects, a model of a three-locus signal transduction network is also analyzed. It is found that genetic dominance as well as overdominance may be an intra- as well as interlocus interaction phenomenon. In the latter case the dominance phenomenon is intimately connected to either feedback-mediated epistasis or downstream-mediated epistasis. It appears that in the intra- as well as the interlocus case there is considerable room for additive gene action, which may explain to some degree the predictive power of quantitative genetic theory, with its emphasis on this type of gene action. Furthermore, the results illuminate and reconcile the prevailing explanations of heterosis, and they support the old conjecture that the phenomenon of dominance may have an evolutionary explanation related to life history strategy.

THE concepts of additive, dominance, and epistatic genetic variance of a metric character keep a central position within the theoretical machinery of quantitative genetics used in such fields as plant and animal breeding, evolutionary biology, medicine, and psychology (Lande 1988; Falconer 1989; Lynch and Walsh 1998). Today, the estimation of these variance components is normally based upon performance covariances between relatives. However, modern quantitative genetic theory, in the form of the presently available statistical models used for estimation of variance components, has conceptually not in principle moved beyond what may be developed from a single-locus model with two alleles, one dominant and one recessive, in a random mating population (Falconer 1989; Kearsey and Pooni 1996; Lynch and Walsh 1998). In fact, the traditional way of developing this mathematical-statistical machinery is to start from the concepts of additive and dominant gene actions, introduce a linear approximation in the form of a least-squares regression of genotypic value on gene content in the single-locus case, define the statistically motivated terms average effect (or breeding value; A) and dominance deviation (D), and from this develop expressions for the variances of A (V_A) and D (V_D) as a function of allele frequency and the degree of dominant gene action (d). This in turn allows establishment of the highly instrumental allele frequency-independent relationship between the abovementioned performance covariances between relatives and V_A. By assuming random mating and independent segregation of loci, the single-locus results are valid for the multilocus case without any further theoretical development. From this foundation, expressions for epistatic variance are developed (Lynch and Walsh 1998).

Cheverud and Routman (1995) stressed the importance of differentiating between physiological and statistical definitions of dominance and epistasis. By making this distinction they showed that as physiological dominance (d) contributes to both the additive genetic and dominance values and variances, physiological epistasis contributes to additive genetic, dominance, and interaction genetic values and variances. Thus there is a tight conceptual connection between the definitions of additive, dominant, and epistatic gene action in the physiological sense and the terms additive, dominance, and epistatic variance in the statistical sense. However, we by no means have a clear mechanistic understanding of the underlying causes of these phenomenological definitions of gene action at the molecular genetic level, how these are related, and in which way they generate and contribute to the various variance components. In

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this sense we are far from having a real quantitative genetic theory connecting the behaviors of genes to the statistical descriptors of genetic variation at the population level.

The use of quantitative genetic theory with its emphasis on additive genetic variance has been a highly successful enterprise within animal and plant breeding. Despite the fact that physiological dominance and epistatic gene effects contribute to the additive genetic variance, it is fair to say that the theory is mainly built upon the premise of intra- and interlocus additive gene effects, *i.e.*, that allelic effects on the genotypic value of a metric character can be summed within and over loci. It remains to be explained why and how gene regulatory networks and signal transduction pathways, with all their nonlinear interactions and hierarchical organization, behave in such a way that the linear "bean bag model" of quantitative genetics has such a predictive power when implemented within a statistical methodological apparatus.

Part of the explanation may be found if we are able to establish a conceptual bridge between mechanistic regulatory biology in a wide sense and the generic phenomena of quantitative genetics. That is, if we are able to construct regulatory models catching the essential features of regulatory networks behind metric characters that produce these phenomena, we may be able to understand under which regulatory conditions they are realized. Such construction work is strongly motivated by available quantitative trait loci (QTL) data showing that rather few factors appear to be responsible for the major portion of observed selection responses in animals and plants (see, for example, Long *et al.* 1995; Prioul *et al.* 1997).

Here we address this question in a very simple way, but we are able to show that the actual phenomena are generic features of regulatory networks. We show by analytical and numerical means that genetic dominance and overdominance may be intra- as well as interlocus interaction phenomena and that dominance is closely linked to epistatic gene action. However, it appears that in the intra- as well as the interlocus cases there will be considerable room for additive gene effects. It appears that our model framework allows a deeper insight into the molecular basis of, and the relationship between, additive, dominant, and epistatic gene action than what can be achieved within the metabolic pathway framework presented by Kacser and Burns (1981). Finally, we are able to illuminate and reconcile the prevailing explanations of heterosis (Davenport 1908; East 1908; Shull 1908; Stuber *et al.* 1992; Xiao *et al.* 1995), as well as confirm the old conjecture that the phenomenon of dominance may have an evolutionary explanation related to life history strategy (Fisher 1928a,b; Wright 1929a,b; Charlesworth 1979; Orr 1991; Grossniklaus *et al.* 1996; Porteous 1996; Mayo and Burger 1997). We think our approach may be instrumental for developing an empirically sound causal theoretical foundation of quantitative genetics.

MATERIALS AND METHODS

Model structures: Here we consider a gene to be a structural unit composed of a regulatory region and a functional region. Within the regulatory region we include all the DNA of the gene that either directly or indirectly is important for transcriptional, mRNA stability, translational, and posttranslational control of the functional protein. By the functional region we mean the region of the gene that influences the actual function of the protein product. It should be noted that these definitions do not exclude the possibility that part of the regulatory region may physically be located in the actual coding region of the gene.

Our intention is to show how the generic phenomena of dominance, overdominance, additivity, and epistasis can be created from very simple diploid regulatory interaction structures and how the phenomena are related. The models are sufficiently complex to catch most of the molecular mechanisms suggested by Wilkie (1994) to be responsible for generating dominant mutations, such as reduced gene dosage, expression or protein activity (haploinsufficiency), increased gene dosage, ectopic or temporary altered mRNA expression, increased or constitutive protein activity, and dominant negative effects. Beyond this we do not pretend to make any sort of exhaustive list of regulatory structures generating these phenomena.

As classical genetics regards the phenomenon of dominance to be generated by intralocus interactions, we have studied two one-locus models, one with a negative autoregulatory feedback loop, and one with a positive autoregulatory feedback loop (Figure 1a). In addition, we have analyzed a model of a three-locus signal transduction network in order to include the phenomena of epistasis and downstream regulatory effects (Figure 1b). The models are relevant for intra- as well as intercellular regulatory systems.

Intralocus interaction: The situation with intralocus regulatory interaction (Figure 1a) is described by a differential equation system expressing the time rate of change of the protein product concentrations x_1 and x_2 from two alleles located at the same locus X,

$$\begin{aligned} \dot{x}_1 &= \alpha_1 R_1(y) - \gamma_1 x_1, \\ \dot{x}_2 &= \alpha_2 R_2(y) - \gamma_2 x_2, \end{aligned} \tag{1}$$

where $y = x_1 + x_2$ is the total gene product concentration, α_1 and α_2 are the maximum production rates, $\gamma_1 > 0$ and $\gamma_2 > 0$ are the relative degradation rates, and R_1 and R_2 ($0 \leq R_j \leq 1$) are the production regulatory functions for the two alleles of the gene. We assume R_1 and R_2 are continuous and differentiable functions of y and all their parameters. This model is a "diploid" version of the "haploid" gene regulatory models investigated in detail by Glass (1975a,b), Snoussi and Thomas (1993), Mestl *et al.* (1995), Plahte *et al.* (1998), and others. If the two equations have identical parameters and rate functions, the system describes a functional homozygous locus. If at least one parameter or the function in the first equation is different from the corresponding parameter or function in the second equation, the system describes a heterozygous locus.

If R_j, $j = 1, 2$ are monotonically decreasing, Equations 1 represent a one-locus model with negative feedback. If R_j, $j = 1, 2$ are monotonically increasing, Equations 1 represent a one-locus model with positive feedback. In both cases we have assumed that the protein made from the nonpolymorphic functional region of each allele binds monomerically or multi-

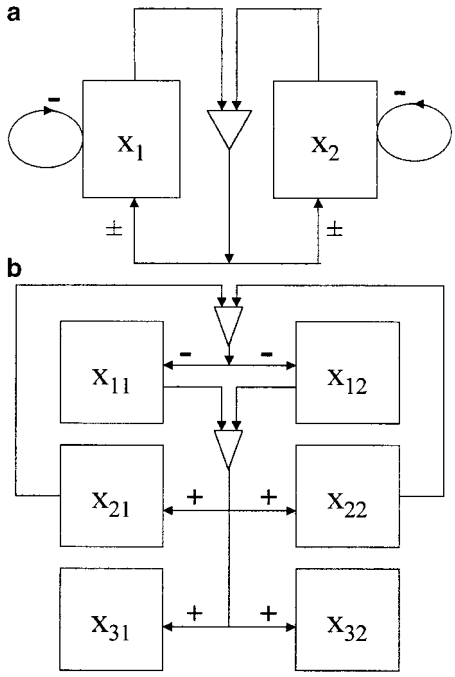

Figure 1.—Connectivity diagrams for the models investigated. (a) Intralocus interaction model. The boxes denoted X_1 and X_2 represent the two alleles of a gene X. The triangle indicates that the concentrations of the gene products x_1 and x_2, from allele 1 and allele 2 at locus X, are added and that the total sum $y = x_1 + x_2$ regulates the activity of the gene by binding to the regulatory region of X. The regulation can be negative ($--$) as well as positive ($++$). (b) Interlocus model. Two possibly polymorphic loci X_1 and X_2 interact by their gene products through a negative feedback loop, and X_1 positively regulates the possibly polymorphic locus X_3. The triangles indicate that the outputs of the gene products x_{i1} and x_{i2}, $i = 1, 2$, are added and that the total sums $y_i = x_{i1} + x_{i2}$ regulate the activities of the three genes. For clarity, the loops representing the decay terms have been left out in this case.

merically to the two polymorphic regulatory regions. The regulation may be at the level of transcription, translation, or post-translation. In the positive autoregulatory case we also presume that there is no polymorphism in the additional regulatory region and in the regulatory gene(s) controlling the initial onset of the production of the protein product (which is operative until the gene product has reached a concentration by which it can stimulate its own production).

We have investigated these intralocus models in the range between two extreme regulatory situations characterized by all regulatory interactions being based, respectively, on a switch-like effect-response mechanism (Bray 1995; Pawson 1995; Lefstin and Yamamoto 1998) and an ordinary Michaelis-Menten mechanism. We use the common Hill function $S(x, \theta, p) = x^p/(x^p + \theta^p)$ as the regulatory function (Hill 1910). When $p \to \infty$, S approaches the unit step function with threshold θ, while when $p = 1$, it describes an ordinary hyperbolic Michaelis-Menten function. Thus we exemplify the negative autoregulatory functions by

$$R_j(y) = 1 - S(y, \theta_j, p_j), \quad j = 1, 2, \tag{2}$$

while the positive autoregulatory ones are exemplified by

$$R_j(y) = S(y, \theta_j, p_j), \quad j = 1, 2, \tag{3}$$

where in both cases $\theta_1 < \theta_2$ by convention.

The equilibrium values y^{11} and y^{22} of the protein product y for the two homozygous genotypes, and y^{12} of the heterozygous genotype (based on Equations 1), are solutions of

$$y^{11} = 2\frac{\alpha_1}{\gamma_1}R_1(y^{11}), \tag{4a}$$

$$y^{12} = \frac{\alpha_1}{\gamma_1}R_1(y^{12}) + \frac{\alpha_2}{\gamma_2}R_2(y^{12}), \tag{4b}$$

$$y^{22} = 2\frac{\alpha_2}{\gamma_2}R_2(y^{22}), \tag{4c}$$

respectively. Define $k > 0$ and put $\mu_j = k(\alpha_j/\gamma_j)$. Then Equations 4a–4c are transformed into

$$ky^{11} = 2\mu_1 R_1(y^{11}), \tag{5a}$$

$$ky^{12} = \mu_1 R_1(y^{12}) + \mu_2 R_2(y^{12}) \tag{5b}$$

$$ky^{22} = 2\mu_2 R_2(y^{22}). \tag{5c}$$

Keeping all parameters except k fixed, a whole range of different situations can then be illustrated by plotting the graphs of the left side and right side of each equation in a single diagram. The equilibrium values are then given by the intersection of the line ky with the graph of the right side.

From the equilibrium values y^{11}, y^{12}, y^{22} the degree of dominance (d) for this locus may be found. Following Falconer (1989), it is given by

$$d = \frac{y^{12} - \bar{y}}{|y^{22} - \bar{y}|}, \tag{6}$$

where $\bar{y} = (y^{11} + y^{22})/2$. When $d = 0$, the locus is said to show additive gene action (additivity), when $0 < |d| < 1$ it shows negative or positive partial dominance, when $|d| = 1$ it shows negative or positive complete dominance, and when $|d| > 1$ it shows negative or positive overdominance.

Interlocus interaction: The situation with interlocus regulatory interactions (Figure 1b) is described by a differential equation system describing the time rate of change of the protein products in a three-locus signal transduction network with two loci X_1 and X_2 connected in a negative feedback loop by monomeric or multimeric binding and one downstream locus X_3 monomerically or multimerically activated by y_1 only, all loci having nonpolymorphic functional regions. Let $x_{ij}, i = 1, \ldots 3, j = 1, 2$ be the concentration of the gene product of locus X_i and allele number j, and define

$$y_i = x_{i1} + x_{i2} \tag{7}$$

as the total gene product of locus X_i. Assuming that X_1 is negatively regulated by y_2 and X_2 is positively regulated by y_1, our general model for X_1 and X_2 is

$$\dot{x}_{1j} = \alpha_{1j}R_{1j}(y_2) - \gamma_{1j}x_{1j}, \tag{8}$$

$$\dot{x}_{2j} = \alpha_{2j}R_{2j}(y_1) - \gamma_{2j}x_{2j},$$

where R_{1j} and R_{2j} are monotonically decreasing and increasing, respectively. For X_3 we assume

$$\dot{x}_{3j} = \alpha_{3j}R_{3j}(y_1) - \gamma_{3j}x_{3j}. \tag{9}$$

This general model structure is exemplified by

$$R_{1j}(y_2) = 1 - S(y_2, \theta_{21j}, p_{21j}), \tag{10a}$$

$$R_{2j}(y_1) = S(y_1, \theta_{12j}, p_{12j}), \tag{10b}$$

$$R_{3j}(y_1) = S(y_1, \theta_{13j}, p_{13j}). \tag{10c}$$

The equilibrium values of the protein products are then solutions of

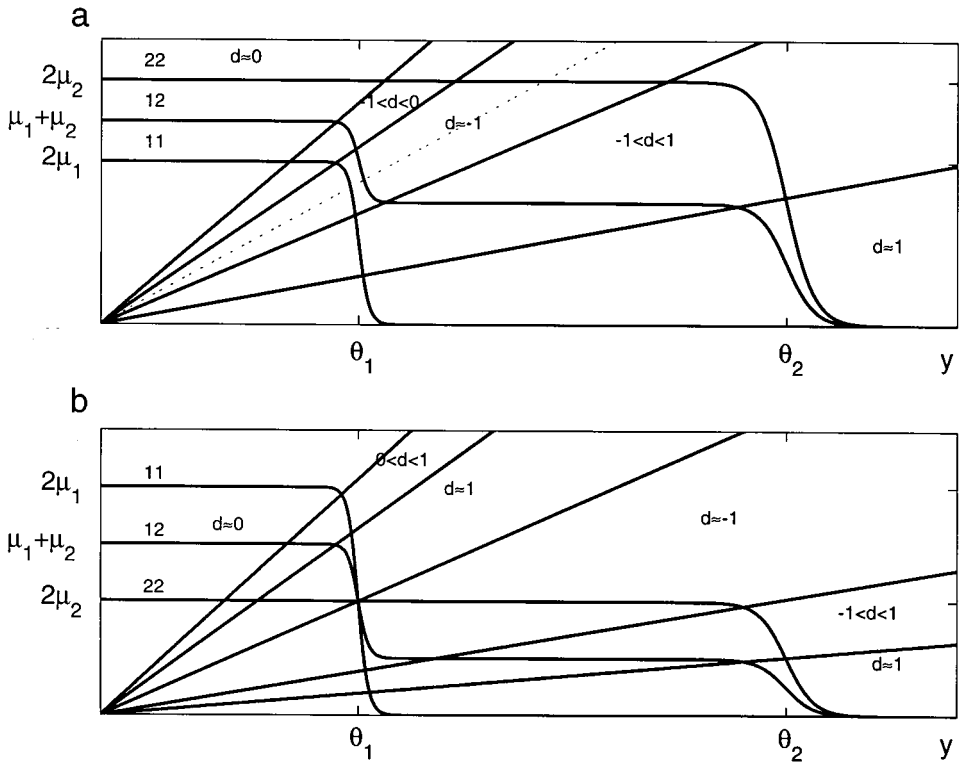

Figure 2.—Intralocus interaction. Graphical representation of the equilibrium solutions for y in the intralocus negative feedback case. The equilibrium values y^{11}, y^{12}, and y^{22} are the abcissas of the intersections of the line ky (exemplified by the dotted straight line in a) with the curves marked 11, 12, and 22, respectively. These curves are the graphs of the right side of Equations 5. The solid straight lines are drawn as guides to the eye to separate sectors with different dominance values. Note that the y-value of the curve (12) is always the average of the values of the two other curves. Curves are drawn for quite steep sigmoids, but the steepness can be slackened to realistic values without corrupting the qualitative picture. All solutions are stable. By convention $\theta_1 < \theta_2$. (a) The case $\mu_1 < \mu_2$ with parameter values $\mu_1 = 2$, $\mu_2 = 3$, $\theta_1 = 3$, $\theta_2 = 8$, $p_1 = 50$, $p_2 = 50$; (b) The case $\mu_1 > \mu_2$ with parameter values $\mu_1 = 4$, $\mu_2 = 2$, $\theta_1 = 3$, $\theta_2 = 8$, $p_1 = 50$, $p_2 = 50$. Near the line separating the sectors $d \approx -1$ and $d \approx 1$, d is poorly defined, and the concept of dominance loses its meaning.

$$y_1 = \mu_{11}(1 - S(y_2, \theta_{211}, p_{211})) + \mu_{12}(1 - S(y_2, \theta_{212}, p_{212})), \quad (11a)$$

$$y_2 = \mu_{21}S(y_1, \theta_{121}, p_{121}) + \mu_{22}S(y_1, \theta_{122}, p_{122}), \quad (11b)$$

$$y_3 = \mu_{31}S(y_1, \theta_{131}, p_{131}) + \mu_{32}S(y_1, \theta_{132}, p_{132}), \quad (11c)$$

where $\mu_{ij} = \alpha_{ij}/\gamma_{ij}$. Each y_i has three genotypic states y_i^{11}, y_i^{12}, and y_i^{22}, as in the one-locus case. Equations 11a and 11b can be solved graphically in much the same way as was used in the one-locus case, and the solution is unique for each allelic combination. To investigate the dominance relationships further, we have run Monte Carlo simulations for the solutions of Equations 11a and 11b for a range of values of μ_{ij} and θ_{ijk}.

RESULTS

Intralocus interaction and negative autoregulation: When R_j is given by Equation 2, Equations 1 have a single, stable state for each of the three genotypes. Dominance is the rule, and the degree of dominance d varies as a function of the parameter values. Overdominance never occurs. However, there is a region in parameter space where $\theta_1 > \text{Max}(2\alpha_1/\gamma_1, 2\alpha_2/\gamma_2)$ in which $d \approx 0$ (Figure 2). In biological terms this implies that additive gene action is only present in the case when the negative feedback loop is not activated for any of the genotypes, and there is only constitutive expression and no intralocus interaction.

Let both of the slopes be steep at the threshold. First let $\mu_1 < \mu_2$. Then d will be close to 1 if $\gamma_2\theta_2 < \alpha_2$, as y^{11} will stay close to θ_1 and y^{12} and y^{22} stay close to θ_2 (Figure 2a). For another parameter domain complete negative dominance ($d \approx -1$) will be the case. For a wide range of mutations affecting production and decay rates the stable states, and thus the dominance patterns, will be robust because the equilibrium states are locked to the threshold (Plahte *et al.* 1998).

If $\mu_2 < \mu_1$ (Figure 2b, remember that $\theta_1 < \theta_2$ by convention), there is a region where d switches from ≈ 1 to ≈ -1, which is quite different from the behavior displayed in Figure 2a. When the sigmoidal interactions are made more gentle and approach a hyperbolic Michaelis-Menten regulation, the borders of the domains in Figure 2 will be less distinct, d values will decrease in magnitude (*i.e.*, one will get partial dominance, $|d| < 1$), and the robustness property is gradually lost. The degree of dominance displayed by the locus will then be more sensitive to mutational changes affecting the production and decay rates of the protein product.

Furthermore, if $\mu_2 < \mu_1$, there is a region in parameter space where y^{11}, y^{12}, and y^{22} are approximately equal for steep as well as quite gentle sigmoidal interactions (Figure 2b). In this region the concepts of dominance and additivity break down, and we have phenotypic stasis despite the presence of functional genetic variation. This is even more prevalent when $\theta_1 = \theta_2 = \theta$, as the steady-state protein concentration will then stay close to θ for all three genotypes as long as $\theta < 2\mu_2$.

Intralocus interaction, positive autoregulation: Now

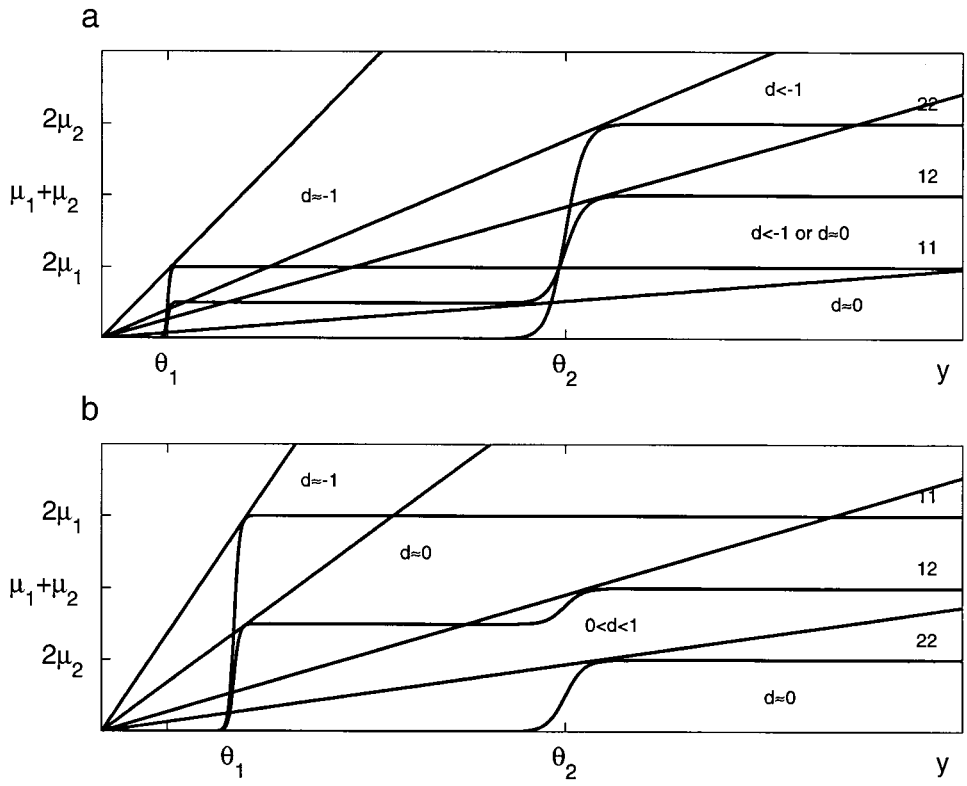

Figure 3.—Intralocus interaction. Graphical representation of the equilibrium solution for y in the intralocus positive feedback case (notation and interpretation are the same as in Figure 2). In this case $y^{11} = 0$, $y^{12} = 0$, and $y^{22} = 0$ are always solutions. In addition, there may be one or more nonzero solutions. Solutions are asymptotically stable if and only if the curve intersects the line ky from above the line to below the line when y increases. (a) The case $\mu_1 < \mu_2$ with parameter values $\mu_1 = 0.5$, $\mu_2 = 1.5$, $\theta_1 = 1$, $\theta_2 = 7$, $p_1 = 50$, $p_2 = 50$. Note that in one sector there is multistationarity and there are two different dominance values. There are no nonzero solutions if $k\theta_1 > 2\mu_1$, *i.e.*, $\theta_1 > 2\alpha_1/\gamma_1$. In this case the bounded production capacity is insufficient to compensate for the degradation. (b) The case $\mu_1 > \mu_2$ with parameter values $\mu_1 = 1.5$, $\mu_2 = 0.5$, $\theta_1 = 2$, $\theta_2 = 7$, $p_1 = 50$, $p_2 = 50$. Here, there is no multistationarity for positive solutions. For the same reason as given in a, there are no nonzero solutions if $k\theta_2 > 2\mu_2$, *i.e.*, $\theta_2 > 2\alpha_2/\gamma_2$.

R_j are given by Equation 3. Contrary to the negative autoregulatory case, additive gene action is the prevalent pattern, but there is also ample room for dominant gene action (Figure 3). For each of the three genotypes there will in general be several equilibrium states, some of which are stable. If $\mu_1 < \mu_2$, there is a region where there are two possible stable solutions of y^{12}, one that gives approximate additive gene action and one that gives negative overdominance; *i.e.*, y^{12} is smaller than both y^{11} and y^{22} (Figure 3a). Which one will be realized in a given situation depends on the circumstances. In addition, there is a parameter region exhibiting only negative overdominance. This pattern will prevail even for quite gentle sigmoidal interactions ($p = 2$). When $\mu_2 < \mu_1$, we see that the allele X_2 behaves as a dominant negative mutation ($y^{22} = y^{12} = 0$) in the region where $|d| \approx -1$ (Figure 3b). This pattern is quite robust to changes in the steepness of the sigmoidal interactions. However, there is no overdominance in the regulatory setting behind Figure 3b.

Interlocus interaction: We first consider the loci X_1 and X_2 and the general model given by (8) and (9) with monotonic regulatory functions. Linear stability analysis and the Routh-Hurwitz criteria for stability show that there are only unique and asymptotically stable solutions for y_1 and y_2 for all three genotypes. When only one of the loci is polymorphic, overdominance is not possible. However, additive as well as negative and positive dominant gene action patterns are possible (some patterns are given in Figure 4). The less steep the functional regulatory relationships become, the less complete will the dominance be. With both loci polymorphic all gene action patterns can be realized, including overdominance, for both loci. However, the overdominance will be present in only one locus at a time. To check the proportion of cases with approximate additivity, dominance, and overdominance in d_1 and d_2 in a more systematic way, we ran a series of Monte Carlo simulations for the specific model given by (11a) and (11b). We used various Hill coefficients (p-values) in the range 1–5 and with a 5-fold range in the values for θ_{ij} and μ_{ij}. Motivated by the fact that genetic dominance will be difficult to detect when d is low, we defined additive gene action to be the case if $|d| \leq 0.25$ and dominance to be the case if $0.25 < |d| \leq 1$. A rough estimate is that with polymorphism in either locus 1 or locus 2 there is ~45–55% additivity, ~45–55% dominance, and ~5–10% overdominance in y_1. For y_2 the corresponding percentages are 50–60%, 30–35%, and 10–15%, respectively.

At this point it is important to note that the dominance behavior is not due to intralocus interaction but to interlocus interaction, *i.e.*, epistasis, because the steady-state protein product concentrations of y_1 and y_2 are interdependent. In fact, dominance appears to be present for both loci even if only one of them is polymorphic (Figure 4a). In biological terms this means that if the X_2 locus is polymorphic and the y_1 protein product concentration is assayed, one would observe that the X_1

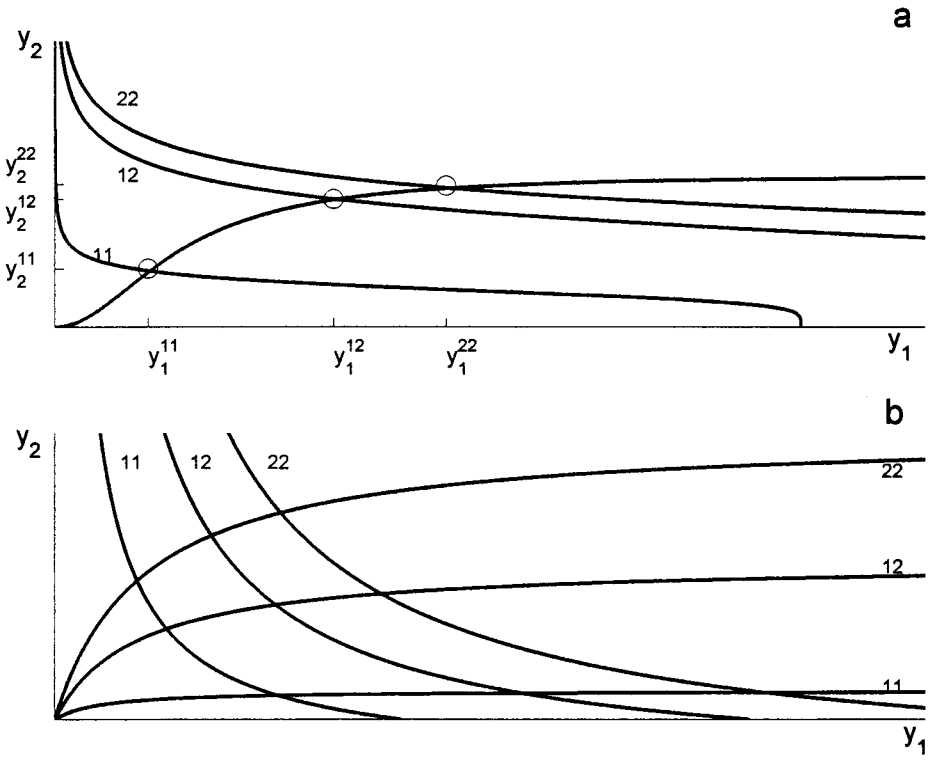

Figure 4.—Interlocus interaction. Graphical solution of Equations 11a and 11b. The intimate relationship between the dominance and epistasis concepts is shown. (a) Polymorphism in X_2 only with parameter values $\mu_{11} = 4$, $\mu_{12} = 4$, $\theta_{211} = 1$, $\theta_{212} = 1$, $p_{211} = 2$, $p_{212} = 2$, $\mu_{21} = 3$, $\mu_{22} = 12$, $\theta_{121} = 2$, $\theta_{122} = 5$, $p_{121} = 5$, $p_{122} = 5$. The three decreasing curves are the graphs of (11a) for the two homozygotes (curves 11 and 22) and the heterozygote (curve 12). The increasing curve is the graph of (11b). The equilibrium y-values are the coordinates of the three points of intersection. (b) Polymorphism in both X_1 and X_2 with parameter values $\mu_{11} = 1$, $\mu_{12} = 10$, $\theta_{211} = 1$, $\theta_{212} = 2$, $p_{211} = 1$, $p_{212} = 1$, $\mu_{21} = 4$, $\mu_{22} = 12$, $\theta_{121} = 3$, $\theta_{122} = 4$, $p_{121} = 1$, $p_{122} = 1$. The decreasing curves are the graphs of the right side of (11a) for the three genotypes of X_2 and vice versa for the three increasing curves. The decreasing (increasing) curves are equally spaced in the y_1-direction (y_2-direction). The equilibrium values are the coordinates of the nine points of intersection. Thus, in this particular example we can have nine possible genotypes. A variety of different patterns can be generated within the same regulatory structure. There can be additivity, partial or full dominance, or overdominance in either variable, but not overdominance in both.

locus showed dominance and erroneously attribute this to intralocus interaction in X_1. For reasons given below in the discussion we call this *an epistatic feedback-mediated genetic dominance effect.*

Now consider the expression pattern of the protein product y_3 of the downstream locus X_3 given by (11c). When X_1 and X_2 are nonpolymorphic, polymorphism in X_3 results in strictly additive behavior independent of the degree of steepness of the regulatory effect-response relationships involved. With upstream genetic variation, the downstream locus may show *apparent dominance* as well as *apparent overdominance* due to epistasis even if it is completely nonpolymorphic (Figure 5). This implies that a dominance effect may be mediated through a number of other loci in a regulatory network. This type of epistasis, which we have chosen to call *a downstream-mediated epistatic genetic dominance effect* (validated below), indicates that a regulatory locus high up in a hierarchy may generate dominance effects through epistasis in loci coding for structural gene products realizing metric characters. With monotonic regulatory functions [(8) and (9)], any degree of dominance displayed by the X_1 locus can be accentuated or even reversed, depending on the form of the function $y_3(y_1)$.

Considering the ubiquity of hierarchy and feedback in regulatory networks we predict that these two types of epistasis phenomena will be frequently encountered and that these distinctions may be of instrumental value when interpreting mRNA and protein expression levels of specific candidate genes within biomedicine as well as animal and plant breeding.

When the lowest equilibrium value of y_1 is much greater than the threshold concentration where y_1 turns on y_3, all allelic variation at the X_3 locus will result in approximate additive behavior. These features of the downstream locus show how additive gene action can be a generic property of highly nonlinear hierarchic regulatory networks.

DISCUSSION

Possible objections to our approach: Even though our model framework is biologically relevant, it might be objected that some of the premises should have been relaxed to catch a broader range of possible regulatory and genetic situations. We have done some preliminary studies where the regulatory interactions are mediated through the decay terms instead of the production terms, and the results appear to be quite similar. We have not yet made any studies of the patterns we will get if the functional regions are equipped with genetic variation too. We do not think, however, that inclusion of this type of variation would change our main conclusions, and it is worthwhile noting that Wang *et al.* (1999), by examining nucleotide polymorphism in *teosinte-branched*1 (a gene involved in maize evolution), found

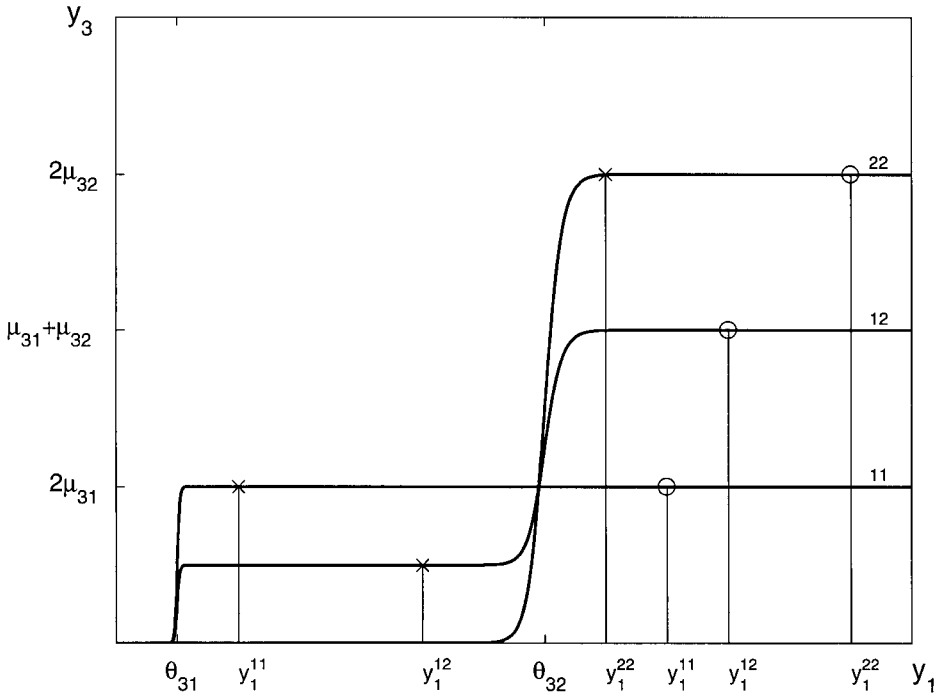

Figure 5.—Interlocus interaction and effect on downstream loci. A graphical representation of (11c) with parameter values $\mu_{31} = 0.5$, $\mu_{32} = 1.5$, $\theta_{131} = 1$, $\theta_{132} = 7$, $p_{131} = 50$, $p_{132} = 50$. Many different combinations of additivity and dominance in X_1 and X_3 are possible. Two different situations illustrating this are shown. Additivity in X_1 might lead to overdominance in X_3 (solution marked by crosses), or dominance in X_1 could lead to additivity in X_3 (solution marked by open circles). When the equilibrium values of all three y_1 genotypes are greater than the largest threshold by which y_1 activates X_3, mutational activity changing the production and decay rates of y_3 will cause only additive gene action.

that the effects of the long-term selection to which maize has been exposed have been limited to the gene's regulatory region and cannot be detected in the protein-coding region.

Even though we have not specifically addressed modeling of allele-dependent regulatory systems, our models can easily be extended to include various types of regulatory interactions associated with such systems (Hollick and Chandler 1998). In any case, if it turns out later on that relaxation of some premises will cause some changes in our results, this will not change our main conclusion, which is that it makes sense to embark on a research program aimed at building a conceptual bridge between regulatory biology and the phenomena of classical genetics.

One might object that we have not made proper use of the concepts dominance and epistasis by introducing the terms *epistatic feedback-mediated genetic dominance effect* and *epistatic downstream-mediated genetic dominance effect*, and that we should restrict the use of the physiological dominance concept to the case of intralocus autoregulatory interaction only. However, our results imply that there are likely to be many phenotypic patterns attributed to genetic dominance that are not based on intralocus interactions. Cheverud and Routman (1995) were able to arrive at the same conclusion within the framework of classical genetic theory, which is quite encouraging from the point of view of making the above-mentioned conceptual bridge. If one restricts the use of the dominance concept to intralocus interaction one would have to rename dominance patterns as nonadditive patterns. There would then be nonadditive expression patterns caused by intralocus positive or negative interactions that might be called genetic dominance patterns, and nonadditive expression patterns caused by interlocus negative or positive feedback interactions or interlocus downstream positive or negative actions. In this way one could not use the dominance concept properly without access to a molecular genetic knowledge that is at present beyond reach in most cases. By introducing the terms suggested above one can use the dominance concept in a consistent way, while at the same time recognizing that genetic dominance may have an intralocus as well as an interlocus basis. In addition, these concepts also contribute to the clarification of the relationship between dominance and epistasis as well as a much needed qualification of the epistasis concept (Phillips 1998).

Classical metabolic control analysis and the prevailing explanation of genetic dominance: Kacser and Burns (1981) proposed an explanation for genetic dominance based on properties of metabolic systems. They showed that dominance of the wild type over null alleles is an inevitable consequence of the kinetic properties of n-enzyme metabolic pathways when studied within the framework of metabolic control analysis (MCA). The explanation for this is mainly based on the so-called summation theorem in MCA, which states that the sum over all enzymes of control coefficients for a flux is unity (Kacser and Burns 1973). There will usually be several enzymes in a given metabolic pathway, so the summation theorem implies that the majority of control coefficients will be small. As there is a hyperbolic relationship between flux and enzyme activity, recessivity of null mutants is an automatic consequence. This theory seems to be widely accepted as the explanation of genetic

dominance (Turelli and Orr 1995; Keightley 1996; Porteous 1996). Savageau (1992), however, challenged this explanation by providing several examples of relevant biochemical systems for which use of the summation theorem to explain dominance is wrong. Thus even for ordinary metabolic pathway systems, some doubt might be expressed about the general validity of the explanation provided by Kacser and Burns (1981; see also Grossniklaus *et al.* 1996).

Some additional comments may also be attached to this prevailing theory or explanation of genetic dominance as it is presented in Kacser and Burns (1981). We think that because the underlying mathematical framework is somewhat restricted:

1. *It cannot provide a general explanation of why recessive mutants are so common.* From systematic mutagenesis of a variety of diploid organisms it is found that the majority of mutations are recessive to wild type. For example, insertional inactivation by random integration of retroviral DNA into the mouse genome produces recessive and dominant phenotypes with a ratio of ~10–20:1 (Jaenisch 1988; Friedrich and Soreano 1991). Insertional inactivation is likely to influence several loci coding for genes engaged in, for example, transcriptional, translational, and posttranslational control; hormone-receptor interactions; and signal transduction pathways instead of n-enzyme substrate-transforming metabolic pathways. This implies that the classical MCA framework is too constrained to catch a broad class of regulatory situations influenced by mutagenesis, where a metabolic flux is not so much the issue as the (temporary) maintenance of intra- and intercellular equilibrium values of key regulatory proteins or hormones. Thus, following Savageau (1972), we suggest that recessivity of mutants is a consequence of natural selection for system designs that are minimally sensitive to mutational alteration. If this is correct, recessivity of mutants is a generic property of robust biochemical regulatory networks in general and will have to be explained by use of a mathematical framework encompassing most of the mechanisms encountered in regulatory biology.
2. *It cannot predict genetic dominance to be an intralocus interaction phenomenon.* Within the framework of quantitative genetic theory, genetic dominance in the physiological sense is described and modeled as an intralocus interaction phenomenon without any further mechanistic interpretation or elaboration (Falconer 1989). In fact, it is one of the main underlying premises of the mathematical-statistical machinery, and this seems to be taken for granted within the quantitative genetics community (Falconer 1989; Henderson 1989; Hoeschele 1991; Kearsey and Pooni 1996). Even though an interaction within a statistical framework in general will have another biological interpretation than an interaction within a mechanistic framework (Lewontin 1974), the two interpretations would have to correspond in the intralocus case. We have shown that in accordance with the classical explanation, the phenomenon of genetic dominance in the physiological sense may indeed be due to an intralocus interaction. However, in addition we predict the existence of feedback-mediated epistatic genetic dominance effects and downstream-mediated epistatic genetic dominance effects. If such an intimate relation between dominance and epistasis turns out to be real, it will raise some challenges for quantitative and population genetic theory. Cheverud and Routman (1995) showed that much epistasis at the gene action level actually shows up as dominance and additive variance at the population level and that very little of it remains as epistasis in the statistical sense. Our work extends this argument even further by disclosing an intimate relationship between dominance and epistasis at the mechanistic level.
3. *It cannot predict the appearance of dominant mutations.* According to Wilkie (1994), it is dominance, rather than recessiveness, that demands special explanation. While cases of dominant or partially dominant ($0 < |d| < 1$) mutations are far outnumbered by recessives, a theory aimed at explaining dominance must be able to explain their occurrence. In addition, disorders due to dominant mutations outnumber recessives by a ratio of ~4:1 (Wilkie 1994).Within our model framework, the occurrence of dominant mutations (including the important group of dominant negative ones) can easily be explained in single-locus as well as multilocus regulatory situations. Wilkie (1994) stated that there are insufficient molecular data to attempt an elaboration of the differences in mechanism giving rise to partial dominance and complete dominance. We have shown that depending on the allelic variation, complete dominance or partial dominance may be realized within all regulatory structures investigated.
4. *It cannot provide a general explanation for the existence of functional recessive homozygotes.* A recessive homozygote within a n-enzyme metabolic pathway context is likely to have a dysfunctional phenotype due to a severe decrease of the flux of the end product (Kacser and Burns 1981). We predict the existence of robust dominance patterns characterized by a functional steady-state value also for the recessive homozygote. Such a pattern is, for example, well documented at the level of protein expression in maize (Leonardi *et al.* 1988; Damerval and De Vienne 1993; Damerval *et al.* 1994), and it is probably present in many other organisms as well.
5. *It cannot predict the phenomenon of overdominance.* However, we have shown that the phenomenon of genetic

overdominance is a generic property of certain single-locus and multiloci regulatory networks.

It should be emphasized that the classical MCA framework has been improved substantially in the last two decades, and today it can handle more complex situations such as regulatory cascades and modular and hierarchic control (Kahn and Westerhoff 1991; van der Gugten and Westerhoff 1997). However, despite the explicit and detailed counter examples to the classical MCA explanation of genetic dominance provided by Savageau (1992), and given the importance that has been attached to this explanation in the genetic literature, the phenomenon of genetic dominance has not been addressed within this extended MCA framework. It is beyond the scope of this article to evaluate how well this framework is able to handle the above objections. Moreover, to the extent that the modern MCA theory relaxes the empirically restricted premises of the original MCA theory, it appears that these new premises and the conclusions that follow from them will have to approach those of a more general framework like biochemical systems theory (BST; Savageau 1969, 1971; Sorribas and Savageau 1989; Shiraishi and Savageau 1992), and our comments to the frequently cited explanation of dominance provided by the classical MCA theory *as such* remain unchanged.

Heterosis is a robust emergent feature of regulatory networks: According to Geiger (1988), classical and more recent analyses of generation means in several animal and crop species clearly demonstrate that genetic dominance in some form is by far the most important component of heterosis. The two earliest hypotheses regarding heterosis, the dominance hypothesis (Davenport 1908) and the overdominance hypothesis (East 1908; Shull 1908), both based on single-locus theory, have competed for most of the last century. Only recently, with the introduction of allozyme markers, restriction fragment length polymorphisms, and high density molecular linkage maps, has it been possible to produce data allowing critical assessments of these hypotheses. However, the issue does not seem to be settled. Stuber *et al.* (1992) observed that heterozygotes for almost all the quantitative trait loci (QTL) for yield in maize had higher phenotypic values than the respective homozygotes. On the other hand, on the basis of data from an intersubspecific cross of rice, Xiao *et al.* (1995) suggested that dominance may be the basis of heterosis in rice.

Recently, the importance of genetic dominance as the most important component of heterosis has been challenged by Yu *et al.* (1997). They investigated the genetic basis of heterosis in an elite rice hybrid by using a molecular linkage map with 150 segregating loci covering the entire rice genome. Overdominance was observed for most of the QTL for yield and also for a few QTL for the component traits. However, correlations between marker heterozygosity and trait expression were low, indicating that the overall heterozygosity made little contribution to heterosis. On the other hand, digenic interactions were frequent and widespread, and the results provide evidence that epistasis plays a major role as the genetic basis of heterosis. For example, a large positive overdominance effect was present at QTL *gp5* at chromosome 5 (marked by the G193x locus) interacting with a locus on chromosome 6 (G342 locus). The overdominance marked by the G193x locus was dependent on genotypes at the G342 locus. The heterozygote of G193x was superior only when the G342 was heterozygous or homozygous for the Zhenshan 97 allele and was intermediate when G342 was homozygous for the Minghui 63 allele (Yu *et al.* 1997).

A connection between epistasis and dominance has also been reported in maize. De Vienne *et al.* (1994) found that epistatic interactions were involved in the control of 14% of the proteins investigated in maize coleoptile extracts. Doebley *et al.* (1995) found that two QTL with large effects on the aspects of plant and inflorescence architecture that distinguish maize and teosinte (being probably the loci for *teosinte branched* and *terminal ear1* plus *tassel replace upper-ear*1, respectively) showed that maize alleles behaved in a more dominant fashion in maize background relative to teosinte background and that these QTL interact epistatically.

It is encouraging to observe that our model framework and our results provide a platform by which the dominance, overdominance, and epistasis hypotheses may be reconciled to some degree. A one-locus negative autoregulatory structure is capable of generating dominance, and a positive autoregulatory one is capable of generating dominance as well as overdominance. That one-locus regulatory structures may be the real genetic basis of some heterosis observations has been empirically confirmed (Hollick and Chandler 1998). On the other hand, through our notions of *feedback-mediated epistatic genetic dominance and overdominance effects* and *down-stream mediated epistatic genetic dominance and overdominance effects* we have shown that in many-locus regulatory networks the concepts of dominance and overdominance are intimately connected to the concept of epistasis. Thus heterosis may also be due to dominance or overdominance effects mediated by epistatic interactions realized within the same regulatory structure.

When two lines are inbred, they are likely to end up with a high degree of homozygosity at several regulatory loci with different types of alleles at some of these loci. The first generation hybrid line will be heterozygous for all these loci. Depending upon the selection history and the allelic variation available before the selection started, one may end up with heterosis that can be attributed either to dominance or to overdominance. As long as both phenomena can be realized within the same regulatory structure, we predict that crossings between different lines selected for the same character

may in some cases show heterosis due to dominance and in other cases show heterosis due to overdominance. Thus, we suggest that the two hypotheses explaining heterosis that have been with us since 1908 are both right to some extent. They do not account for the possibility that dominance patterns may be due to epistasis, however, so the picture is more complex. The genetic basis of heterosis is made up of the genetic regulatory structures controlling the actual metric character. The heterosis phenomenon as such may be attributed to genetic dominance or overdominance effects at one or several loci mediated by feedback loops or downstream signal transduction pathways. Thus, in some sense at the mechanistic level, heterosis may still be claimed to be caused in part by genetic dominance effects even when epistasis is involved. In any case, as more and more detailed genetic information about regulatory interactions becomes available, this shows the necessity of qualifying the epistasis concept into definitional categories reflecting the types of regulatory mechanisms involved (Phillips 1998).

Hybrid lines displaying additive genetic behavior: Even in F_1 hybrids additive inheritance is found in a substantial number of cases (Leonardi *et al.* 1988; Damerval *et al.* 1994; De Vienne *et al.* 1994). Our results show that there exist broad parameter domains where regulatory networks will display additive gene action, so that this type of gene action is to be expected even if there are several nonlinear actions present in an actual network. In addition comes the fact that in signal transduction networks where regulatory proteins control the expression of structural proteins downstream, a downstream protein *z* may, for example, display additive inheritance when the concentration of its regulatory protein *y* stays constantly above the threshold where it transcriptionally, translationally, or posttranslationally activates the production of *z*.

Genetic dominance and life history strategies: Since the contributions by Fisher (1928a,b, 1929, 1931, 1934) and Wright (1929a,b, 1934) there has been a debate whether the phenomenon of genetic dominance needs an evolutionary explanation or not (Charlesworth 1979; Kacser and Burns 1981; Orr 1991; Grossniklaus *et al.* 1996; Porteous 1996; Mayo and Burger 1997). We suggest that the opposing views, but not necessarily the actual explanations given, may be reconciled to some degree. First, it is necessary to qualify what is meant by an evolutionary explanation. If the robustness property of biochemical networks causes the phenomenon of genetic dominance due to recessivity of mutants, and robust biochemical network designs have been selected for, the widespread occurrence of dominance as a genetic phenomenon has an evolutionary explanation at the bottom (we call it type I explanation in the following). The same argument applies to dominance patterns caused by dominant mutations. However, genetic dominance patterns as such may be selected against, they may be selectively neutral, or they may be selected for. Dominance patterns due to the existence of recessive lethal or sublethal alleles are likely to be selected against. However, if they are selectively neutral or are selected for, an additional evolutionary explanation is needed (type II explanation). If these two situations are to be meaningfully discussed within the context of the principle of natural selection, one will have to explain why a genetic dominance pattern is not the only option for the types of regulatory networks realized in living organisms. It is encouraging that we are in principle able to provide such a rationale. We have shown that there may be several situations where a regulatory structure might realize a dominance pattern or an additive pattern and that there exist broad parameter domains (*i.e.*, allelic variation domains) for the additive as well as the dominance regimes. If these results are experimentally confirmed, a type II evolutionary explanation may be needed.

In fact, available empirical data seem to call for a type II explanation. The classical genetic approach predicts that strong directional, and to some degree stabilizing, selection usually erodes only additive genetic variance while not affecting dominance variance (Felsenstein 1965; Lande 1988; Turelli 1988). Crnokrak and Roff (1995) actually found that traits for wild species closely associated with fitness (life history) had significantly higher dominance components than did traits more distantly related to fitness (*e.g.*, morphology). Merila and Sheldon (1999) extended this by showing that fitness-related traits tend to have low heritabilities compared to nonfitness traits not because of lower additive variances (indeed they tend to be higher) but rather because of much higher nonadditive variances.

It would be interesting to qualify these insights even further by grouping the species providing the underlying data behind the conclusions in Crnokrak and Roff (1995) and Merila and Sheldon (1999) into two categories characterized by the production of a small and a large number of young progeny per lifetime, respectively. Fitness traits, including dominant gene actions as described above, will show increased genetic variation of the progeny in a sexually reproducing population. By reducing genetic dominance the performance of the progeny with respect to these fitness traits will be more predictable and more narrowly centered around the mid-parent value. Within the context of stabilizing selection, this is a strategy that might pay off when, due to life-historical reasons, an organism produces only a few progeny during its lifetime. On the other hand, if the organism produces large numbers of progeny that later on are exposed to an unpredictable abiotic and biotic environment, it may be more advantageous to let the progeny display as much genetic variation as possible.

However, if this grouping offers no further insight, the available empirical data show in any case that the high genetic dominance variances of the fitness charac-

ters in wild species may be caused by selection for dominant gene actions *per se* and not something that is left after most of the additive variance due to additive gene action has been eroded. Our results give a mechanistic rationale for this without invoking different types of gene regulatory architectures between fitness and nonfitness traits (Merila and Sheldon 1999), the concept of *dominance modifiers* [which is apparently still in active use (Bourguet 1999)], or any other type of additional mechanism or principle beyond what we already know about the functioning of gene regulatory networks.

Conceptual bridge between regulatory biology and quantitative genetics: Numerous successful breeding experiments confirm that animal and plant genomes are organized in such a way that metric characters are more or less normally distributed, that offspring normally resemble their parents, and that a unidirectional selection normally results in a selection response for many generations. These are necessary prerequisites for natural selection to work, and, at present, we can only conjecture that natural selection has favored a genomic regulatory organization realizing these properties as they contribute to the evolvability of metric characters. The effectiveness of animal and plant breeding programs implies that the estimation apparatus of quantitative genetics, through its concept of additive genetic variance, catches these generic properties to a considerable degree, even though this does not appear to reside in consistent definitions and concepts with great explanatory and heuristic power at the genetic level (Kempthorne 1977). Even though the establishment of quantitative genetic theory from an empirically sound mechanistic regulatory biology involves much more than what we have provided here, our results indicate that the attempt to link the conceptual apparatus addressing dynamic phenomena at the molecular genetic level with the statistically orientated conceptual apparatus addressing phenomena at the population level may be rewarding.

Almost all efforts to study the genetic basis of metric characters, and to use this information in practical breeding work, are based on the QTL approach where molecular genetic information is analyzed by a mathematical-statistical methodology (Prioul *et al.* 1997; Lynch and Walsh 1998). However, we think that this methodology is unable to provide a real causal understanding of how a metric character is regulated. This is because a pure mathematical-statistical explanatory strategy is not the proper language to describe and analyze how emergent dynamic phenomena are generated by the interactions of lower-level systemic entities. But, a conceptual and methodological marriage between mathematical statistics and nonlinear system dynamics may become quite instrumental if it is cultivated within a molecular genetic framework. We predict that such a research program will provide biomedicine, evolutionary theory, as well as animal and plant breeding theory, with some refreshing new insights.

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