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The Evolutionary Ecology of Dominance-Recessivity

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Contents

Introduction 1

Within-Individual Ecology 2

Between-Individual Ecology 3

Evolutionary Dynamics 3

A Numerical Example 5

Evolutionary stops 6

Simulations 10

Dominance-Recessivity at a Housekeeping Locus 12

Discussion 14

References 15

Abstract

An “adaptive dynamics” modelling approach to the evolution of dominance-recessivity is presented. In this approach fitness derives from an explicit ecological scenario. The ecology consists of a within-individual part representing a locus with regulated activity, and a between-individual part that is a two-patch soft selection model. Evolutionary freedom is allowed at a single locus. The evolutionary analysis considers directed random walks on trait space, generated by invasions of mutants.

The phenotype of an individual is determined by allelic parameters. Mutations can have two effects: they either affect the affinity of the promoter sequence for transcription factors, or they affect the gene product. The dominance interaction between alleles derives from their promoter affinities.

I show by means of an example that additive genetics is evolutionarily unstable when selection and evolution maintain two alleles in the population. In such a situation, dominance interactions can become stationary close to additive genetics or they continue to evolve at a very slow pace towards dominance-recessivity. The probability that a specific dominance interaction will evolve depends on the relative mutation rate of promoter compared to gene product and the distribution of mutational effect sizes. Either of both alleles in the dimorphism can become dominant and dominance-recessivity is always most likely to evolve. Evolution then approaches a population state where every phenotype in the population has maximum viability in one of the two patches.

When the within-individual part is replaced by a housekeeping locus that codes for a metabolic enzyme, evolution favours a population of two alleles on the same conditions as for a regulated locus. In the case of a housekeeping gene however, the evolutionary dynamics is attracted towards a population state where the heterozygote and only one homozygote phenotype equal the optimum phenotypes in the two patches.

Key words: dominance interactions – ESS – adaptive dynamics – long-term evolution – soft selection

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The Evolutionary Ecology of Dominance-Recessivity

Tom J.M. Van Dooren

Introduction

Many have come to accept the position that the recessivity of a lot of mutants is a natural consequence of the kinetics of metabolic networks, and that it needs no selective explanation at all (Wright, 1934, Kacser & Burns, 1981, Keightley, 1996). Metabolic Control Theory (Kacser & Burns, 1973) provides the accepted explanation for the recessivity of null alleles at loci that code for metabolic enzymes: Although the gene activity from that locus is halved, the effect on metabolic phenotype is small. The kinetic coupling of sequential reaction steps compensates for the loss in catalytic activity. However, dominance-recessivity does not occur at loci coding for metabolic enzymes alone (Wilkie, 1994, Bourguet & Raymond, 1998). It even occurs in genes that play a decisive role in pattern formation during embryonic development. For instance, handedness in scale-eating cichlids is probably determined at a single locus with one dominant and one recessive allele (Hori, 1993). Such determination of handedness in an individual needs to be done only once and at an early stage of development.

I present a single-locus long-term evolutionary model for the evolution of dominance interactions between alleles. The model is of a regulated gene that is activated at some point in development, allowed to perform its function and subsequently put to rest. The absence of gene dosage effects on biochemical activity in many pivotal developmental regulators (Hodgkin, 1993), can be explained by a mechanism where the total amount of gene product produced from such a locus is approximately fixed.

The modelling procedure is rather straightforward and uses an adaptive dynamics approach, which is a dynamic extension of the ESS approach (Dieckmann & Law, 1996, Metz et al. 1996). The coexistence of alleles at the locus is modelled and this leads to a phenotype recipe that maps vectors of allele parameters to phenotypes. Individuals interact ecologically through their phenotypes. From the combined individual-ecological model, invasion probabilities of mutant alleles in a resident population of one or several alleles can be estimated. The evolutionary analysis considers the evolutionary random walks in trait space generated by these invasion probabilities. The model is compared with an equivalent one where the regulated locus is replaced by a housekeeping locus.

Within-Individual Ecology

The total amount of gene product the locus is allowed to produce is regulated. That occurs by means of regulation of transcription (Lewin, 1997), or, for instance, through regulation of mRNA degradation (Brawerman, 1993). The two alleles at this locus therefore find themselves in a situation known in population ecology as a resource competition scenario. They compete in this "within-individual" ecology for transcription until they reach the quota of transcription their locus is allowed.

Alleles are parametrized by two-dimensional vectors $X = (x,y)$, $x,y \in \mathbb{R}^+$, and phenotype recipe $f(X_i, X_j)$ (1) maps the traits of allele pairs to their phenotype.

$$f(X_i, X_j) = \frac{y_i}{y_i + y_j} x_i + \frac{y_j}{y_i + y_j} x_j \tag{1}$$

The first parameter x specifies for example the colour of the gene product, or another aspect of the gene product that can vary in a continuous manner. The second parameter y derives from the promoter sequence. It stands for the affinity of the promoter sequence for transcription factors, hence the recruitment of RNA polymerase (Ptashne & Gann, 1997). In a diploid eukaryote with two alleles, the promoter affinities determine the average proportion in the total pool of gene product that will originate from each allele (see Flavell (1989) for an example relevant to such a situation). As a consequence, the scalar phenotype (1) is a weighted average of both gene product parameters x. The weights depend on the proportional recruitment of RNA polymerase by the promoters of the respective alleles. I assume that sampling effects on recruitment can be neglected and that genetically identical individuals express the same phenotype.

Null alleles with zero affinity are always recessive. With sufficient transcription, we get the phenotype $f(X_i, X_i) = x_i$ in homozygotes. This "allelic value" equals the gene product parameter. Phenotype recipe (1) can be rearranged for heterozygotes as

$$f(X_i, X_j) = \frac{x_i + x_j}{2} + \frac{y_i - y_j}{2(y_i + y_j)}(x_i - x_j) \tag{2}$$

The phenotype recipe (2) is split into an additive term and a second term due to the deviation caused by a dominance interaction. The dominance interaction $d(X_i,X_j)$ between ordered alleles X_i and X_j equals $\frac{y_i - y_j}{2(y_i + y_j)}$. When $d(X_i,X_j)$ is positive, the first argument allele X_i (partially) dominates, and the second argument allele is (partially) recessive. Equal promoter affinities imply a dominance interaction equal to zero and additive genetics. Full dominance/recessivity occurs when the absolute value of d is 0.5.

Overdominance for phenotype is not possible here. I do not allow for zero promoter affinities either, assuming that the null homozygote is not viable. Therefore, promoter affinities can never lead to complete dominance or recessivity, but it is assumed that they allow dominance interactions close to that (i.e., d lies in the open interval $]-0.5,0.5[$).

Between-Individual Ecology

A two-patch version of Levene's soft selection model is used (Levene, 1953, Cannings, 1971, Kisdi & Geritz, submitted). After random mating of gametes in a common pool and random dispersal, zygotes settle with equal probability in one of both patches. Juvenile individuals experience within each patch a round of viability selection on phenotype, with viabilities S^1 in the first patch and S^2 in the second patch, where

$$S^i(x) = e^{\frac{-(x-T_i)^2}{2\sigma^2}} \tag{3}$$

The parameter σ^2 is strictly positive and describes the strength of selection, the parameters T_i correspond to the phenotypes of maximum viability in the patches. In the next step, within each patch, a proportion of the carrying capacity is assigned to each phenotype, according to its proportional occurrence after selection. Both patches are equal in carrying capacity and are always occupied at maximum density. Individuals do not differ with respect to fecundity, and gametes are produced in abundant quantities. This ecological scenario leads to a population dynamical equation in discrete time. The recursion relation for the frequency p_i of an allele X_i in a population of n alleles has the following form:

$$p_i' = p_i \left[0.5 \frac{\sum_j^n p_j S^1(f(X_i, X_j))}{\sum_j^n \sum_k^n p_j S^1(f(X_j, X_k))} + 0.5 \frac{\sum_j^n p_j S^2(f(X_i, X_j))}{\sum_j^n \sum_k^n p_j S^2(f(X_j, X_k))} \right] \tag{4}$$

All attractors of this population dynamics are point equilibria (Cannings, 1971).

Evolutionary Dynamics

The equations describing evolution among monomorphic populations are the same as those describing the evolution of a single trait (see below), and can be found in Geritz et al. (1998, haploid model). I assume that an evolutionary random walk starts from an initial population with a single allele.

Mutant alleles are initially rare. As a consequence, they predominantly occur as heterozygotes and their frequency of occurrence is negligible in comparison with the frequencies of residents. The growth rate $\zeta(M, R_1, R_2, ..., R_n)$ of a mutant allele $M = (x_M, y_M)$ in a population dynamical attractor of n different resident alleles R_i ($i = 1...n$) is called invasion exponent or mutant fitness (Metz et al. 1992, Rand et al. 1994, Geritz et al. 1998). It can be calculated as

$$\zeta(M,R_1,R_2,\ldots,R_n) = \ln\frac{p_M}{p_M}, = \ln\left[0.5\frac{\sum_i^n p_i S^1(f(M,R_i))}{\sum_i^n\sum_j^n p_i p_j S^1(f(R_i,R_j))} + 0.5\frac{\sum_i^n p_i S^2(f(M,R_i))}{\sum_i^n\sum_j^n p_i p_j S^2(f(R_i,R_j))}\right] \quad (5)$$

Here p_M stands for the frequency of the mutant allele. A mutant allele can only invade if $\zeta(M, R_1,R_2,\ldots,R_n)$ is larger that zero. When the mutant allele equals one of the resident alleles, ζ is zero. Because of their initial rarity, mutant alleles inevitably suffer the effects of demographic stochasticity. The probability for a successful invasion in a fixed background of residents can be approximated as 2ζ, using the theory of branching processes, on the condition that the value of ζ is close to zero (Ewens, 1969).

When the residents are of a single allele type R, the invasion exponent $\zeta(M, R)$ equals the invasion exponent of a phenotypic model (Geritz et al. 1998, Van Dooren, in press), where the mutant phenotype $f(M,R)$ probes the resident with allelic value

$$r = f(R,R) \quad (6)$$

The local fitness gradient for the mutant allelic value in a monomorphic resident population with allele R and allelic value r is (Geritz et al. 1997, 1998)

$$\frac{\partial\zeta(M,R)}{\partial x_M}\Big|_{M=R} = \frac{1}{\sigma^2}\left(\frac{T_1+T_2}{2} - r\right) \quad (7)$$

This fitness gradient is positive for resident allelic values below $r^* = \frac{T_1+T_2}{2}$, and negative for resident allelic values above. Trait values where a fitness gradient is zero are called evolutionarily singular points (Metz et al. 1996, Geritz et al. 1997, 1998); r^* is such a singular allelic value. Starting from a monomorphic initial population, substitution events in the coding sequence bring the allelic value to this evolutionarily attracting singular value (Metz et al. 1996, Geritz et al. 1998). I assume that mutations in the promoter and the coding region occur independently, and that mutations are sufficiently rare that different mutations never invade together. In a monomorphic resident population, mutations in the promoter alone do not affect the scalar phenotype of the mutant heterozygote. The promoter DNA-sequence is therefore subject to drift only.

When we fix the resident phenotype at the singular allelic value, the invasion exponent (5) is approximately a parabolic function of the mutant trait, with its extremum at the singular point. Provided that this extremum is a maximum, the singular allelic value is an Evolutionarily Stable Strategy and evolution stops there. With a local minimum, the singular point becomes a branching point. Close to such a branching point, a successful invasion in an initially monomorphic resident population leads to permanent coexistence of the progenitor and the mutant, instead of replacement of the former resident by the invading mutant allele (Metz et al. 1996, Geritz et al. 1998). The evolutionary random walk makes from there further substitution steps among populations with two alleles that have different gene product parameters. In each such substitution event, one of the two resident alleles is replaced by an invading mutant allele. In order to have a local fitness minimum at the singular allelic value, the second derivative of the invasion fitness in the mutant allelic value has to be positive,

$$\frac{\partial^2 \zeta(M,R)}{\partial x_M{}^2}\Big|_{M=R} = \frac{1}{4\sigma^2}\left(\frac{(T_1 - T_2)^2}{4\sigma^2} - 1\right) > 0 \tag{8}$$

Condition (8) shows that it depends on the strength of selection and the difference between the optima T_1 and T_2 of the selection functions, whether evolution will halt at a monomorphic population of individuals expressing the ESS gene product parameter, or favour a polymorphism of alleles.

This soft selection model allows dimorphic equilibria that are protected and unique (Kisdi & Geritz, submitted). That means that a pair of alleles *A* and *B* cannot coexist in a resident population unless allele *A* can invade allele *B* and *B* invades *A*. Each resident allele in such a polymorphic resident population has two fitness gradients attached to it, one for its allelic value and a second one for promoter affinity. Only those mutations can invade that change the value of a resident trait such that the product of the fitness gradient for that allele-trait combination times the trait change, is positive. Resident populations that are evolutionary stops (denoted "ES") occur at simultaneous zeroes of all fitness gradients (Metz et al. 1996, Geritz et al. 1997). When some fitness gradients for a resident state are zero, but others not, the evolutionary random walk will proceed in the direction dictated by the non-zero gradient. At an evolutionary stop, all fitness gradients are at a local maximum. If the evolutionary walk is attracted to a resident population state where one or several gradients have a local minimum, branching into a higher order polymorphism occurs (Metz et al. 1996, Geritz et al. 1997). Attraction is essential, because evolutionary branching is a slow process (Dieckmann & Law 1996). Without attraction, an evolutionary random walk will not stay long enough near the singular point for branching to occur. In this model, the evolutionary random walk is essentially a stochastic process visiting monomorphic and dimorphic resident states. From within the set of allele dimorphisms, branching into trimorphisms sometimes occurs in simulations, but after few substitution steps, the resident states become dimorphic again.

A Numerical Example

I discuss an example of the evolutionary dynamics in resident population states of two alleles. In this example, the ecological parameters are set at $T_1 = 8$, $T_2 = 12$, and $\sigma^2 = 1.125$. For these values, there is a monomorphic singular point at allelic value $x = 10$ that allows branching. Starting with a monomorphic population, the evolutionary random walk approaches this branching point and near to it, the resident population becomes dimorphic. The result is that, in an evolutionary random walk, a sequence of dimorphic resident states follows the sequence of monomorphic resident states.

I studied the properties of such evolutionary random walks by means of simulation, but also by the pattern of fitness gradients on the set of possible resident states.

Every dimorphic resident state corresponds to a point in four-dimensional space: two co-ordinates for the allelic values, and two for the promoter traits. A whole collection of sections through that space can be made, with values y_1 and y_2 fixed on each section. However, it appears that only the value of the dominance interaction between both alleles matters in which pairs of alleles can coexist as residents (Van Dooren, in press) and in the pattern of fitness gradients on such sections. This dominance interaction can be specified as the interaction $d(x_S,x_L)$ between the allele with the smallest allelic value

x_S, and the allele with the largest allelic value x_L. It is sufficient to study a stack of slices at different values of this interaction $d(x_S,x_L)$. On them, one can indicate fitness gradients for mutations in gene product parameters x_S and x_L, the trait values specified by the coding sequence, and for y_S and y_L, the promoter dependent trait values. Isoclines delineate regions with different signs for the fitness gradients and correspond to sets of zero gradient values (Metz et al. 1996). Evolutionary stops occur at intersections of all isoclines.

Slices of the set of protected dimorphisms are shown for different values of $d(x_S,x_L)$ (Figures 1-3). Isoclines for y_S and y_L always appear to coincide, and both fitness gradients for the y parameters favour mutants that either increase or decrease the dominance interaction in the same way, irrespective of which resident allele mutates. For instance, when an increase in the promoter affinity y_S of the allele with the smaller allelic value is favoured, only mutants of the other allele causing a decrease in promoter affinity y_L can invade. If either of these mutants replaces its progenitor, that leads to a dimorphism where the allele (x_S,y_S) will dominate (x_L,y_L) more, that is, $d(x_S,x_L)$ increases. One can thus speak of a fitness gradient for the dominance interaction $d(x_S,x_L)$.

Evolutionary stops

On the slice where the two resident alleles interact according additive genetics (Figure 1), there are two singular points that are evolutionary stops for both traits, and an evolutionary saddle point for the gene product trait (Kisdi & Geritz, submitted). That saddle point is at the same time a branching point for the promoter trait y. When the affinity of the promoters evolves before one of these evolutionary stops is hit, neither of both stops ($ES_0$1 nor $ES_0$2) will be reached, and partial dominance is the result. Additive genetics is evolutionarily unstable on this slice. The substitution events that occur in the gene product before the first mutant in the promoter invades, determine whether an increase or a decrease in $d(x_S,x_L)$ will be favoured (Fig. 1).

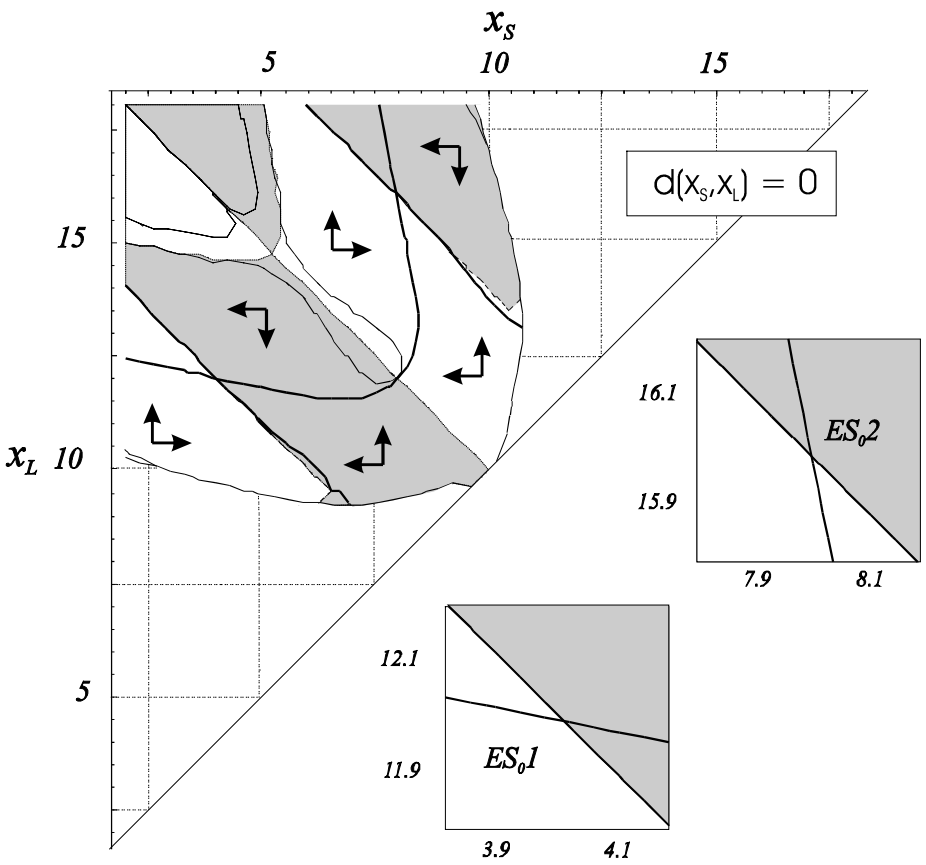

Figure 1. The set of alleles with allelic values x_S, x_L that can coexist when they interact additively ($d(x_S,x_L) = 0$) is drawn in superposition on a grid. The type with the smallest allelic value is found on the horizontal axis, the type with the largest allelic value on the vertical axis. Within the set fitness gradients and fitness isoclines are indicated. The fitness gradients for the gene product are indicated by arrow pairs in each region separated by *x*-isoclines. The fitness gradient for the dominance interaction $d(x_S,x_L)$ is indicated by a colour code. In grey regions this dominance interaction can increase, in white regions it can decrease. The borders of colour coded regions thus coincide with isoclines for the dominance interaction. Thin isoclines of the gene product and dotted edges of colour coded regions correspond to local fitness minima. Thick isoclines correspond to local fitness optima of the gene product trait. The evolutionary walk over dimorphic resident states starts near allelic value pair *(10,10)*. Branching into trimorphisms does not occur. Two triple intersections of isoclines are evolutionary stops. the first one ES_01 lies at allelic values *(4,12)*, the second one ES_02 lies at allelic values *(8,16)*. Insets show blowups of the isocline pattern around these evolutionary stops.

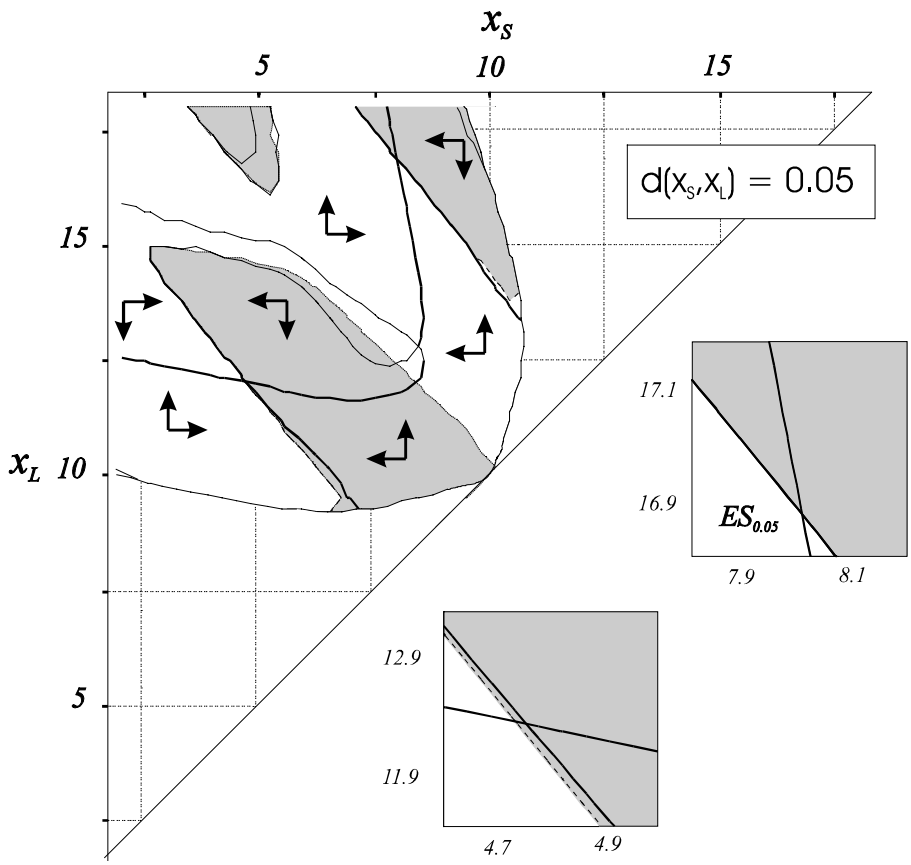

Figure 2. The set of protected dimorphisms at $d(x_S,x_L) = 0.05$ is shown, with the pattern of fitness gradients indicated. For this value of the dominance interaction, there is a single evolutionary stop $ES_{0.05}$ at allelic values *(8,16.87)*. The other reachable singular point for the allelic values does not coincide with an isocline for the dominance interaction. A blow-up of the region around it clarifies this.

As the dominance interaction evolves, which we can imagine as if moving through a stack of slices, isoclines change shape and the singular points found at intersections of isoclines change location (Figures 2 and 3). If we track a singular point for the gene product (at the intersection of the *x*-isoclines) through the stack, it coincides with a *y* isocline only on part of the slices. For small absolute values of the dominance interaction δ, there are two singular points for the allelic values. Figure 2 shows an example. One of them, ES_δ is evolutionarily stable in both traits. In the other singular point, the dominance interaction can continue to evolve. For positive values of δ, the singular point with the pair of largest allelic values is an evolutionary stop (Fig. 2). At negative values of δ, on the other hand, the singular point with the largest allelic values is the one that can be invaded by mutants further decreasing the dominance interaction $d(x_S,x_L)$. As the dominance interaction between resident alleles increases in absolute value, the singular point where the promoter can evolve moves in the direction of the manifold of allelic values $\{x_S= 8, x_L= 12\}$ (Figure 3). That holds true for positive as well as negative values of $d(x_S,x_L)$. On this manifold, the two homozygote phenotypes equal the optimum phenotypes T_1 and T_2. When a sequence of mutations brings the resident state close to the singular point for allelic values where the promoter can continue to evolve, further mutations in both traits move the resident state towards the manifold

$\{x_S = 8, x_L = 12\}$. This steady change will be very slow however, in comparison to the initial approach of the allelic value singular point. All fitness gradients are very small near such a singular point. That implies small invasion probabilities, hence slow evolutionary movement.

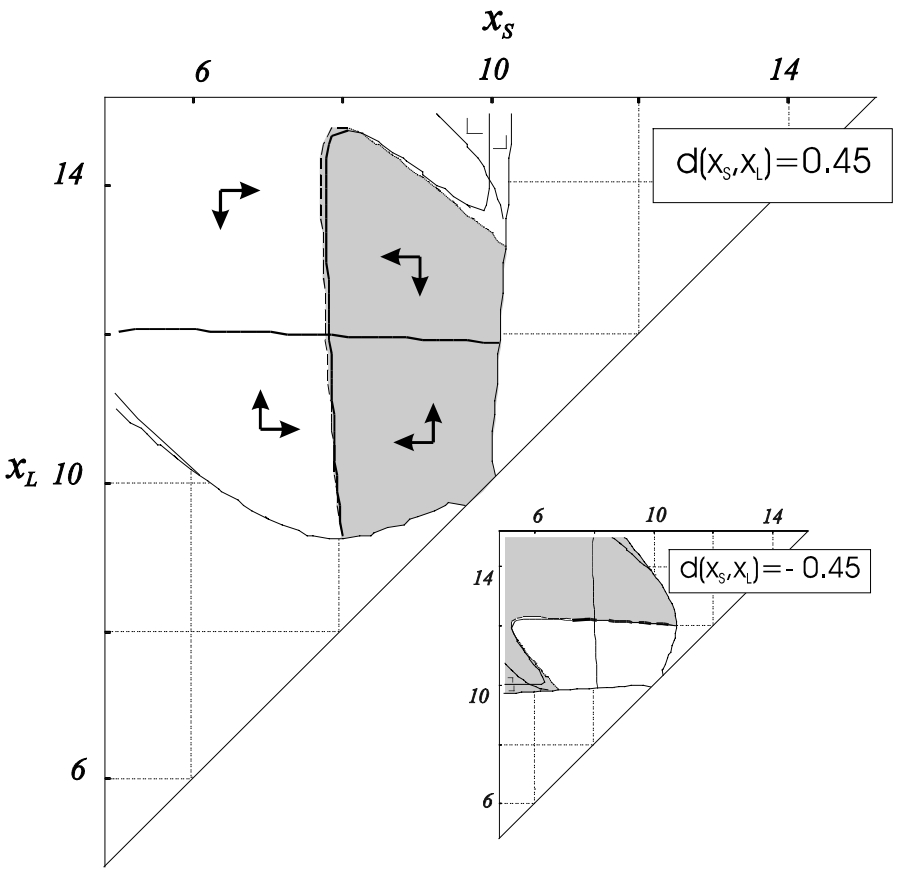

Figure 3. For allele pairs coexisting at $d(x_S,x_L)= 0.45$, a single attracting singular point exists but it is a singular point for allelic values only. It is found at allelic values *(7.85,12)*. That is near the pair of optimum phenotypes *(8,12)*. The inset shows that for alleles coexisting at $d(x_S,x_L) = -0.45$ also, the singular point is situated near the pair of optimum phenotypes.

On the slice at additive genetics, the first mutations in the product can lead the resident state in an alternating fashion through regions were the value of the dominance interaction can either increase or decrease. This can happen as long as the value of $d(x_S,x_L)$ remains small. If no further mutations occur in the promoter, the evolutionary stop for that value of the dominance interaction can be reached. When the absolute value of the dominance interaction increases, these full stops become harder and harder to reach because the isoclines near the saddle point move towards the edge of the set of dimorphisms and narrow the area through which the evolutionary walk must pass on its way to such an evolutionary stop. As soon as the isoclines touch the boundary a single reachable singular point remains (as in Figure 3). The further evolution of the dominance interaction is then assured. The evolutionary walk approaches the allelic values $x_S = 8$ and $x_L = 12$, and the dominance interaction $d(x_S,x_L)$ goes in the direction of

0.5 or -0.5 as far as the promoter affinities allow. The result is that all three phenotypes in the population will come to resemble the two phenotypes T_1 and T_2 that have maximum viability in one of the two patches.

We can conclude that after a sufficiently long period on the evolutionary timescale, the resident state will be at least near to a singular point for the allelic value, and possibly at an evolutionary stop. Further changes in allelic parameters in the coalition occur with low probability. Either of both alleles can become dominant, and after a long period in evolutionary time, every dominance interaction can be expected with a certain probability which can be estimated from simulations. For other choices of ecological parameters $\{T_1,T_2,\sigma^2\}$ that allow branching points, the pattern of fitness gradients implies the same conclusions.

Simulations

Figure 4 shows the distribution of dominance interactions from a number of simulations of evolutionary orbits with fixed length in evolutionary time. At each point in evolutionary time a mutant is generated. The mutational step is drawn from a normal distribution with zero mean and a fixed variance. When a mutation sets an allelic parameter at zero or a negative value, a new mutant is generated. Every mutant is allowed to invade with the probability calculated from the branching process approximation. If it does, the resident state is set at the ensuing population dynamical attractor. Considering possibly successful mutants only, the effects of demographic stochasticity affect evolutionary orbits in simulations in two ways. (i) For a given size of the mutation effect, mutations in the direction of the steepest fitness gradient have a higher probability of invasion. (ii) Mutations in a trait have a higher probability of invasion when they differ more from the same trait in their progenitor. Demographic stochasticity affects the direction an evolutionary random walk takes, and the distribution of substitution step sizes actually occurring. With small (but non-zero) relative mutation rates in the promoter, a probability weight on additive genetics and nearby values is found from simulations of evolutionary orbits, but values close to dominance-recessivity are already most probable (Figure 4a). For every combination of non-zero mutation rates in promoter and product, a scenario with a trait substitution sequence showing a steady increase or decrease in the dominance interaction is more likely than one leading to an evolutionary stop near additive genetics. Figures 4a and 4b show that increasing the relative mutation rate in the promoter decreases the probability that an evolutionary stop near additive genetics is approached. Increasing the variance of the distribution of mutation effects also makes attraction towards one of the evolutionary stops close to additive genetics more probable (simulations not shown). The probability distribution over dominance can also depend on where in allele trait space the resident state became dimorphic. This effect is only important when the distribution of mutation effects is relatively small or fixed. I found no significant effect of initial condition in the simulations presented.

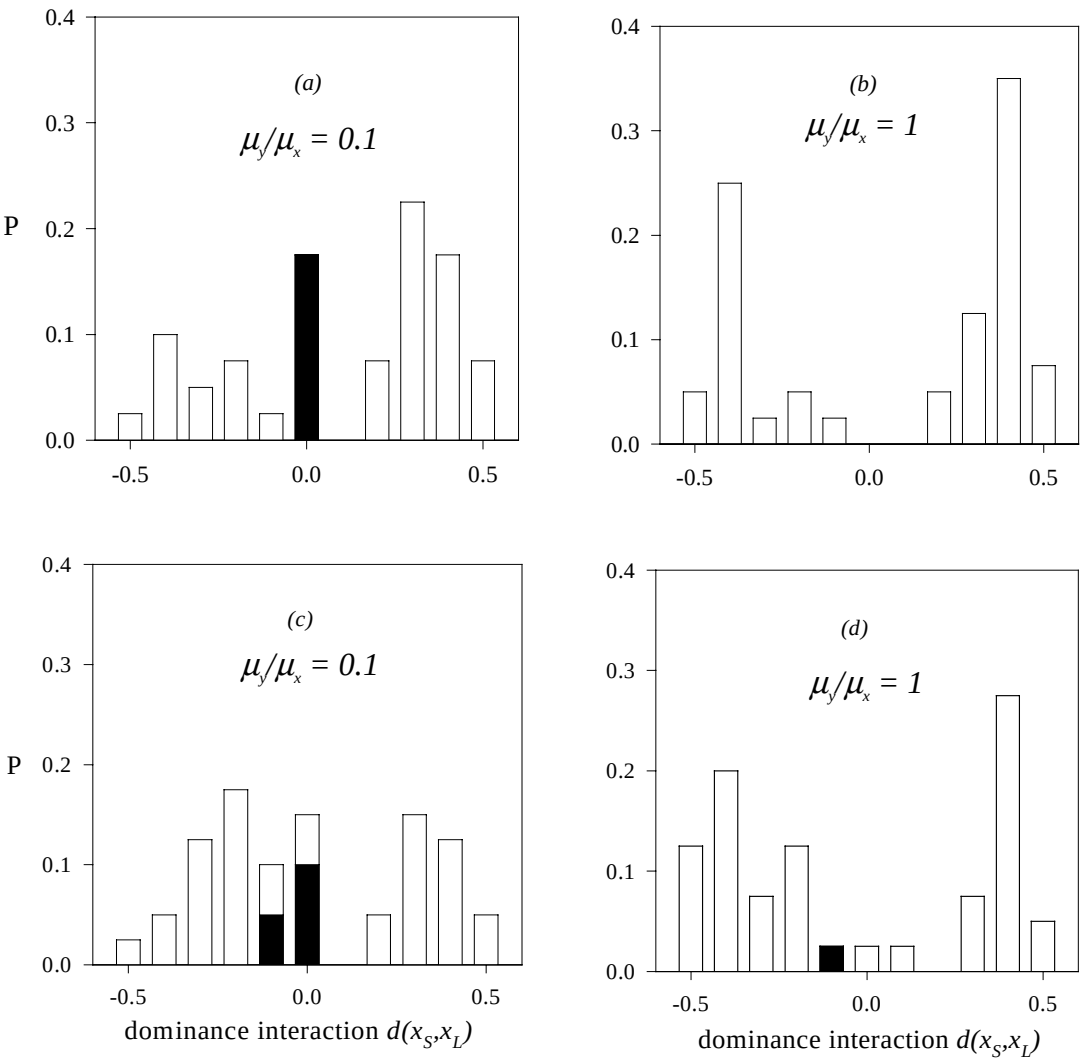

Figure 4. Distributions of dominance interactions from simulations. Per plot 40 evolutionary random walks of 2500 mutation events were simulated. Each mutation effect was drawn from a normal distribution *N(0,0.5)* for both traits. Half of the orbits were initialised at allele *(9,1)*, the other half at *(11,1)*. The relative mutation rates of promoter and gene product μ_y/μ_x are indicated on each plot. Black bars indicate the proportion of simulations that converged to an evolutionary stop near additive genetics. Plots *(a)* and *(b)* are from simulations of the ecological scenario as described in the text. Plots *(c)* and *(d)* are from simulations of the same ecological scenario, except that the probability of assignment to the first patch was set at 0.8.

In the model, gametes are assigned to either of both patches with equal probability. When introducing extreme asymmetry in the probabilities gametes are assigned to either of both patches, the evolutionary conclusions do not change (Figs. 4c and 4d). Either of

both alleles can still become dominant, and dominance-recessivity is approached with a greater likelihood than an evolutionary stop near additive genetics.

Dominance-Recessivity at a Housekeeping Locus

The transcription of housekeeping genes that code for metabolic enzymes, occurs constitutively and these loci are under a common control (Lewin, 1997). Their transcription is regulated by factors that are ubiquitous and not specific. The characteristics of such a gene and its gene product can be summarised by a single parameter, the enzyme activity A_i that in the end results from the amount of gene product transcribed from the allele (Kacser & Burns, 1973). If one allele at a housekeeping locus recruits less transcription and its activity is as a consequence reduced, the other allele does not profit from that. In this within-individual ecology, the resource of transcription factors is not limiting and does not lead to indirect interactions between alleles. Housekeeping genes interact through their gene products that are coupled in a metabolic pathway. The phenotype of an individual can be taken to be the flux through the metabolic pathway in which the gene product functions (Kacser & Burns, 1973).

If we again allow evolutionary freedom at one locus, and if we assume that the genetic background at the other loci involved in the metabolic pathway remains monomorphic, a simple phenotype recipe can be found in Kacser and Burns (1981). It links the enzyme activities A_i, A_j of the alleles at the locus to their flux phenotype in the following manner:

$$f(A_i, A_j) = \frac{c_1(A_i + A_j)}{c_2 + A_i + A_j} \tag{9}$$

The parameters c_1 and c_2 depend on kinetic parameters of the complete metabolic pathway. We can express the activity of an allele as a function of the homozygote phenotype or allelic value x_i it specifies, provided that $c_1 > x_i$:

$$A_i = \frac{c_2 x_i}{2(c_1 - x_i)} \tag{10}$$

Substituting this expression in equation (9), the phenotype recipe becomes a function of the allelic values and of the parameter c_1 ,

$$f(x_1, x_2) = c_1 \frac{\dfrac{x_1}{c_1 - x_1} + \dfrac{x_2}{c_1 - x_2}}{2 + \dfrac{x_1}{c_1 - x_1} + \dfrac{x_2}{c_1 - x_2}} \tag{11}$$

It is possible to write this phenotype recipe as a sum of two terms, where the first term represents an additive contribution of alleles to flux phenotype and the second term a dominance deviation. I used this phenotype recipe in the two-patch soft selection model (4), to obtain a long-term evolutionary model of dominance evolution at a housekeeping locus. In this model one allelic parameter evolves, namely the allelic value.

A monomorphic singular point is again found at the allelic value $r^* = \frac{T_1 + T_2}{2}$. This singular allelic value is a branching point when mutant fitness has a local minimum (on condition (8)), otherwise it is an ESS. Therefore, as well for the housekeeping locus as for the regulated locus, the triple of ecological parameters $\{T_1, T_2, \sigma^2\}$ determines whether a monomorphic or a polymorphic evolutionary stop will be found.

From the pattern of fitness gradients on the set of dimorphic protected polymorphisms, it appears that only dimorphic evolutionary stops are expected. No further branching into trimorphisms occurs. Figure 5 shows these dimorphic evolutionary stops when the ecological parameters are set at $T_1 = 8$, $T_2 = 12$, and $\sigma^2 = 1.125$. For most values of the parameter c_1 there are two evolutionary stops. Only when this parameter is only slightly larger than the allelic values studied, a single evolutionary stop is found. Substitutions at other loci in the pathway can change the value of the parameter c_1, but the pattern of phenotypes at each evolutionary stop is the same. A population state where all three phenotypes resemble the two optimum phenotypes T_1 and T_2 is never reached. At all evolutionary stops, only one homozygote phenotype and the heterozygote phenotype equal the optimum phenotypes. With a regulated locus such a pattern only occurs at evolutionary stops near additive genetics.

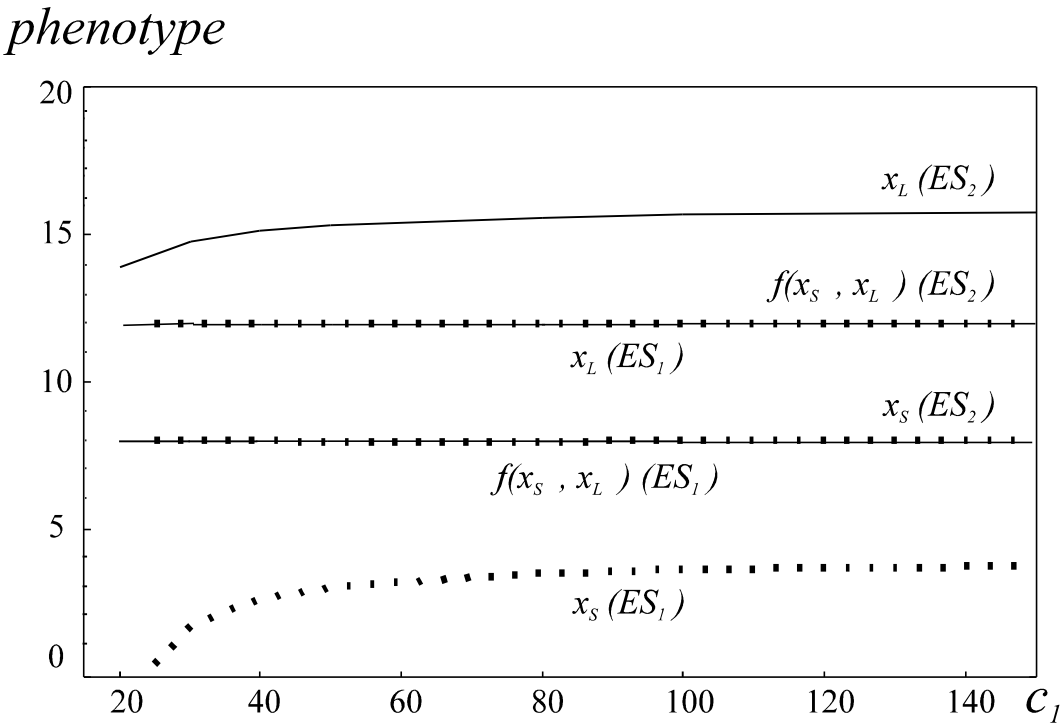

Figure 5. The pattern of dimorphic evolutionary stops for a housekeeping locus, drawn as a function of the metabolic pathway parameter c_1. For most values of the parameter c_1, two evolutionary stops exist (indicated as ES_1 -dotted line- and ES_2-continuous line). Only for small values of c_1, there is a unique dimorphic evolutionary stop (ES_2). Per evolutionary stop, the homozygote phenotype of the allele with the smallest (largest) allelic value is labelled x_S (x_L) the heterozygote phenotype has the label $f(x_S, x_L)$.

Discussion

In this model, the parameters of the ecological scenario determine how the dominance interaction will evolve. When branching occurs and a sequence of dimorphic resident states is generated subsequently, then we see dominance interactions evolve by means of natural selection. Among monomorphic populations, the pattern of change in the dominance interaction results from random genetic drift in the promoter, while selection brings the allelic value towards the mean of the two optimum phenotypes. At a regulated locus as well as a housekeeping locus this pattern of change is expected. The long-term evolutionary picture is clearly a lot richer than Sheppard (1975, p. 170) suggested: *"...if there are only two optimum phenotypes and three genotypes, two of these will come to resemble one another"*. In dimorphic populations, evolution further moulds the phenotypes in the population to the optimum phenotypes in the two patches. It can achieve complete success at a regulated locus, but is expected to succeed only partially for a housekeeping locus. At evolutionary stops for the housekeeping locus, one homozygote phenotype is always different from either of both optimum phenotypes. It is also the case that two housekeeping alleles can only have a dominance interaction close to full dominance-recessivity when one allele has a very small allelic value compared to the allelic value of the other allele (it has to be close to a null allele). I expect for housekeeping loci that evolution will only achieve a population with all three phenotypes at optimum values, when the allelic value of the null allele corresponds to an ecologically optimum phenotype.

With a regulated locus, evolution can halt near additive genetics or the dominance interaction can continue to evolve at a slow pace towards dominance-recessivity. In Bryan Clarke's seminal model for dominance evolution in polymorphic populations, the heterozygotes play a mixed strategy (Clarke 1964). Although mixed strategies are beyond the scope of the present paper, his conclusion that the dominant allele in a dimorphism is in most cases the rarer one (Clarke, 1964), holds in this model in resident states near a singular point for allelic value only. There the equilibrium allele frequency of the dominating allele lies around *0.2-0.3*. It does not hold for the full evolutionary stops found for the regulated locus (with the frequency of the dominating allele around *0.7-0.8*). That, in turn, is in agreement with an expectation from a model by O'Donald (1968). For the housekeeping locus (Fig. 5), the allele with the largest allelic value is more abundant at evolutionary stops indicated by ES_1. At evolutionary stops labelled ES_2, the allele with the smallest allelic value is more abundant. The intuitive explanation here is that the phenotype with the lowest mean viability then always has the smallest probability of occurrence.

The model presented has a modular structure. That makes it easy to modify a separate module, as was done for the phenotype recipe. The evolutionary analysis can be repeated for any phenotype recipe or ecological scenario of choice. The recipes in this paper were chosen because of their appealing simplicity. Undoubtedly many other and more complicated ones are possible. For instance, Biochemical Systems Theory / Metabolic Control Theory (Kacser & Burns, 1973, Savageau, 1975) give well-known phenotype recipes for flux traits in multilocus systems. It is a major challenge, to embed such multilocus genetic systems in various ecologies.

In two-locus models of short-term selection on dominance (Fisher, 1928, Wright, 1929, Feldman & Karlin, 1971, Bürger, 1983), modifier loci were introduced that control the phenotypes at another primary locus. A recurrent criticism on this approach is that a

modifier allele which causes dominance of a wildtype over a deleterious or null allele, has only a very small selective advantage, when the primary locus is close to mutation-selection balance (Mayo & Bürger, 1997). However, dominance modifiers can be successfully selected for in other situations (Mayo & Bürger, 1997). Long-term evolutionary models of two-locus systems with a primary and a modifier locus that are slightly more mechanistic than the previous generation of such models must be feasible as well.

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