

Plasticity, memory and the adaptive landscape of the genotype

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The adaptive value of epigenetic inheritance systems is investigated in a simple mathematical framework. These systems enable the environmentally induced phenotypes to be transmitted between generations. The frequencies of the different epigenetic variants are determined by the plasticity and the efficiency of transmission (called memory). Plasticity and memory are genetically determined. This paper studies the evolution of a quantitative character, its plasticity and memory, on the adaptive landscape. Due to the dual inheritance of the character, selection acts on two levels: on the phenotypes of the same genotype, and on the different genotypes. Plasticity generates the raw material, and memory increases the strength of phenotypic selection. If the character is far from the peak of the landscape, then dual inheritance of the character can be advantageous for the genotype. Near the peak it is more favourable to suppress phenotypic variation. This would lead to genetic assimilation.

Keywords: epigenetic inheritance systems; quantitative character; adaptive landscape; genetic assimilation

1. INTRODUCTION

Evolutionary adaptation proceeds through the selection of hereditary variants. For the process to go on, we must assume the *a priori* existence of these entities. Therefore, the nature of variation and heredity is fundamentally important in evolutionary biology. Predominantly, it is believed that changes in the genetic material are responsible for the existence of variation. But are there any other inheritance systems in addition to the DNA? The answer is a definite 'yes'. One of the first people recognizing this possibility was Sewall Wright (Wright 1945). He proposed the existence of alternative cellular states that can arise without genetic mutations and remain unchanged after reproduction (see also Dean & Hinshelwood 1963). Although Wright had much influence on the further development of population genetics, this idea was forgotten for a long time. The notions of multiple inheritance systems and Lamarckian evolution have been coupled and totally refused. The mechanism of Lamarckian evolution can be summarized in three statements: (i) the change in a character can be induced by the environment; (ii) the induced change can be transmitted to the next generation, even if the inducing environment is no longer present; (iii) the induced phenotypes are adaptive in the given environment.

The 'soft' version of Lamarckism includes only the first two points, the 'hard' version covers all three points. If we agree to the former, we do not think that the environment induces the required phenotypes. Rather, good and bad phenotypes are thought to be induced alike. This paper deals only with the latter possibility.

Experimental facts showing the inheritance of phenotypic variation are scarce, but growing in number. These

variants are mostly not reversed in a predictable manner, and are not as stable as genetic mutations (Jablonka & Lamb 1995). For example, inbred lines of organisms growing in a detrimental environment showed heritable changes in their characters. The changes persisted, even if the organisms were returned to their normal environment (e.g. Francis & Jones 1989; Jablonka & Lamb 1995, pp. 134–135). Sometimes the variation propagated only by asexual mechanisms (Spiegelman *et al.* 1945; Ng 1990), or in cell culture (Meins 1989), but in several cases sexual reproduction is not a real barrier (Brink 1973; Hollick *et al.* 1997; Grewal & Klar 1996; Pillus & Rine 1989). It is remarkable that multicellular organisms also showed heritable phenotypic variation (e.g. Flavell & O'Dell 1990). Selection experiments also strengthen the occurrence of such phenomena. Sometimes inbred strains—that are believed to lack any genetic variability—were able to adapt to new environmental conditions (Brun 1965; Fitch & Atchley 1985; Jablonka & Lamb 1995, pp. 145–146). Because of the low population size in the experiments, the appearance of new, advantageous mutations seems to be very unlikely. Probably, the environment induced phenotypic variation, and the beneficial variants spread in the population.

The systems enabling the transmission have recently been called 'epigenetic inheritance systems' (Maynard Smith 1990; Jablonka & Lamb 1995). These systems have a dual role in evolution. First, they are responsible for the inheritance of functional states in cell lineages during development (see Jablonka *et al.* 1992; Richards 1997; Paro 1990). Second, they enable the organisms to adapt to new environments without genetic changes. The role of epigenetic inheritance systems in ontogeny is widely accepted. On the contrary, their role in adaptation is a

matter of debate. Recently, some theoretical models stated that a random (Jablonka *et al.* 1995), or periodically fluctuating (Lachmann & Jablonka 1996), environment favours the spread of epigenetic inheritance systems. Lachmann & Jablonka (1996) presented some good examples, where special ecological conditions and unusual hereditary systems are coupled. They calculated the optimal rate of switching between two epigenetic variants in temporally changing environments.

In this paper, I deal with continuous phenotypic variation, and examine how an epigenetic inheritance system modifies the evolution of a quantitative character on the adaptive landscape.

2. ENVIRONMENT, PLASTICITY, AND MEMORY

In this section, I examine the effect of the environment on a quantitative, polygenic trait. The environment modifies the phenotypic pattern in two different ways: (i) it generates phenotypic variation; and (ii) it selects the variants. Throughout the paper I restrict my attention to a constant environment. This means that only micro-environmental fluctuation is present, inducing different phenotypes in an unpredictable way, but the optimum phenotype is the same for all microenvironments. The microenvironments can be represented by a random variable (ξ) with mean zero and variance δ_ξ^2 . The microenvironments induce different phenotypes of a given genotype.

In the light of the experimental facts and theories (Waddington 1957; Scheiner 1993; Gavrillets & Hastings 1994), it is obvious that the influence of the environmental deviation cannot be assumed to be independent of the genotypes. Rather, the sensitivity to the microenvironments is determined genetically. In this model I am primarily interested in the effects of the environment on the phenotypic variance of the trait. I assume that the phenotypic distribution of the genotype is Gaussian

$$\phi(y) = \frac{1}{\sqrt{2\pi V_y}} \exp \left[-\frac{(x - y)^2}{2V_y} \right], \quad (1)$$

with mean x and variance $V_y = P\delta_\xi^2$, where x and P are the mean phenotype and plasticity, respectively. The mean phenotype and plasticity characterize one genotype. The variance of the distribution is determined by the microenvironmental variance (δ_ξ^2) and the plasticity (P). In this model, plasticity specifies the sensitivity of the genotype to the microenvironments. By assumption, the microenvironmental variance has no influence on the mean (x). This is a good approximation, if the effect of the microenvironments on any given locus is small (Gavrillets & Hastings 1994). I assume that the Gaussian distribution means the following: plasticity generates random phenotypic variation, so it is not an adaptive response *per se*. Accordingly, I do not assume the hard version of Lamarckian inheritance. Symmetrical distribution assures that the good and bad phenotypes are induced with the same frequency.

If an epigenetic inheritance system is present, then phenotypes are not only generated, but are also inherited. The mean number of generations through which the phenotypes are transmitted is measured by the memory

(m). In the model, plasticity and memory characterize the epigenetic inheritance system from a functional point of view.

The mean phenotype (x), the plasticity (P), and the memory (m), of a given trait are assumed (i) to be determined by the genetic system; (ii) to be genetically independent of each other and any other traits; and (iii) to evolve, like any other character. Within this framework, the genetic system specifies the limiting conditions, i.e. the possible epigenetic states of the genotype. However, the genotype does not specify which transmissible state is actually present in a given individual.

3. THE ADAPTIVE LANDSCAPE AND THE STRATEGIES

How does the epigenetic inheritance system modify the evolution of a quantitative character? When is it advantageous to enlarge, or to suppress, phenotypic variation? More formally, we would like to know how P and m change as x evolves to its optimum. One of the most important factors determining the evolution of a given trait is the relationship between genotype and fitness. This relationship can be represented on an adaptive landscape (Wright 1932, 1980). Originally, the adaptive landscape is a surface in a multidimensional space, showing the mean fitness of the population as a function of possible states of the population (e.g. gene frequency, means of continuous characters). In this paper we are dealing with the adaptive landscape of the genotype. This represents the fitness of the genotype plotted against the possible states of the characters. Any given point of the landscape specifies one genotype. I restrict my attention to the most simplistic case: the evolution of one genetically independent trait. I assume Gaussian stabilizing selection on the character, so the adaptive landscape has only one peak. The fitness of an individual with phenotype y is

$$W(y) = \exp \frac{-(y_{\text{opt}} - y)^2}{2V_s}, \quad (2)$$

where y_{opt} denotes the optimal phenotype, and $1/V_s$ measures the intensity of selection. If we ignore the effect of linkage disequilibrium, or frequency-dependent selection, then the mean phenotype will tend to the maximum. How does selection change the plasticity and memory during the evolution of the mean? To examine this question, we need to define three different genetic strategies (figure 1).

1. The fixed genetic strategy (FS) has one genetically fixed phenotype.
2. The strategy with phenotypic plasticity (PS) has different phenotypes, with frequency determined by $\phi(y)$, but the phenotypes are not inherited.
3. The strategy with memory (MS) shows the same initial phenotypic distribution as PS, but the phenotypes are also transmitted to subsequent generations depending on memory. This strategy possesses an epigenetic inheritance system (range of memory: one to infinity).

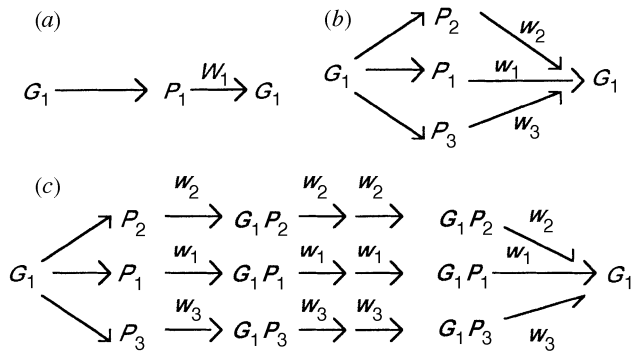


Figure 1. The strategies—each strategy has the same genotype G_1 specifying its position on the adaptive landscape. The fixed genetic strategy (a) has only one fixed phenotype (P_1), and the fitness of the phenotype is W_1 . The plastic strategy (b) can have different phenotypes (P_1, P_2, P_3) with fixed probabilities. The fitnesses of the individuals with phenotype P_1, P_2, P_3 are W_1, W_2, W_3 , accordingly. In the first generation the strategy with memory (c) shows the same phenotypic distribution as the previous one, but the phenotypes are also inherited, so the individuals are G_1P_2, G_1P_1, G_1P_3 , and their fitnesses are W_2, W_1, W_3 , accordingly.

4. THE QUANTITATIVE MODEL

Compare the fitnesses of the three strategies on a given point of the adaptive landscape. This point is the genetically determined phenotype of FS, and the mean phenotype of PS and MS. Defining the fitness of MS is reasonable only if memory is much shorter than the expected time it takes for the character to mutate. Because epigenetic variants seem to be much more susceptible to the environment than genetic ones, this assumption seems to be fulfilled. Accordingly, the time-scales of phenotypic variation and phenotypic selection are different from the time-scale of genetic evolution.

The fixed genetic strategy has only one fixed $y=x$ phenotype, so the fitness of this strategy is

$$W_{\text{FS}}(x) = W(x). \quad (3)$$

The plastic strategy has a continuous distribution of phenotypes, determined by $\phi(y)$. The expected fitness of the genotype with mean x and plasticity P is the weighted average over the fitnesses of the phenotypes

$$W_{\text{PS}}(x, P) = \int \phi(y) W(y) dy. \quad (4)$$

The expected fitness of the strategy with memory is given as follows. The y phenotype is induced with frequency $\phi(y)$ in the first generation. This phenotype is transmitted to subsequent generations specified by the memory. After m generation selection, its frequency is $\phi(y)W(y)^m$. The frequency of the (x, P, m) genotype after m generations is therefore $\int \phi(y)W(y)^m dy$. The expected fitness of the (x, P, m) genotype is the geometric mean over the memory span. We obtain

$$W_{\text{MS}}(x, P, m) = \left[\int \phi(y) W(y)^m dy \right]^{1/m}. \quad (5)$$

It is easy to see that the fixed genetic strategy and the plastic strategy are special cases of the strategy with memory. The former shows no phenotypic variation, so its plasticity is zero, and the memory of the latter is one. Therefore, it is sufficient to analyse equation (5) in order to compare the three strategies. Without loss of generality—possibly by redefining scale—we set $y_{\text{opt}}=0$. Applying equations (1) and (2), the evaluation of equation (5) gives

$$W_{\text{MS}}(x, P, m) = \left[\frac{V_s}{V_s + Pm\delta_\xi^2} \right]^{\frac{0.5}{m}} \exp \frac{-x^2}{2(V_s + Pm\delta_\xi^2)}. \quad (6)$$

It must be stressed that the derivation of equation (6) assumes that the initial phenotypic distribution is normal. In the case of the fixed genetic strategy ($P=0$), equation (6) reduces to equation (2), with $y=x$. We assume, that the mean and the plasticity evolve synchronously on the adaptive landscape, leaving the memory unaltered. Now we can examine the optimal plasticity for a given point of the landscape (x) and for a given memory (m). Solving $\partial \ln W_{\text{MS}}(x, P, m) / \partial P = 0$, we obtain

$$\hat{P} = \left(x^2 - \frac{V_s}{m} \right) \frac{1}{\delta_\xi^2}. \quad (7)$$

Since we cannot interpret negative plasticity biologically, this formula is relevant only if $P \geq 0$. Increasing plasticity is advantageous in the following cases (see equation (7) and figure 2).

- (i) The character is far from the peak of the landscape (x is high). On the peak of the landscape ($x=0$), only the fixed genetic strategy can be optimal. This is due to the fact that in this case plasticity produces only suboptimal phenotypes.
- (ii) The intensity of selection is high. It ensures that the possibility of finding much better epigenetic variants is high.
- (iii) The microenvironmental variance (δ_ξ^2) is low. Microenvironmental variance and plasticity together act as the agents of phenotypic variation ($V_y = P\delta_\xi^2$). If δ_ξ^2 decreases, plasticity has to increase to ensure unchanging phenotypic variation.
- (iv) The memory is long. Memory increases the strength of phenotypic selection. It allows the frequency of a rarely induced, but advantageous phenotype to spread. On the other hand, the plastic strategy ($m=1$) ‘regenerates’ its phenotypic variants in every generation, so they are always present with the same frequency. Epigenetic inheritance systems enable phenotypic variability to be high, even if the intensity of selection is low, and the mean is close to its optimum.

By definition, we find the critical point of the landscape, where the optimal plasticity is zero. As the mean phenotype passes through this point during its evolution, selection forces the suppression of plasticity, so the fixed genetic strategy becomes favourable. From equation (7) we get

$$x_{\text{crit}} = \pm \sqrt{\frac{V_s}{m}}. \quad (8)$$

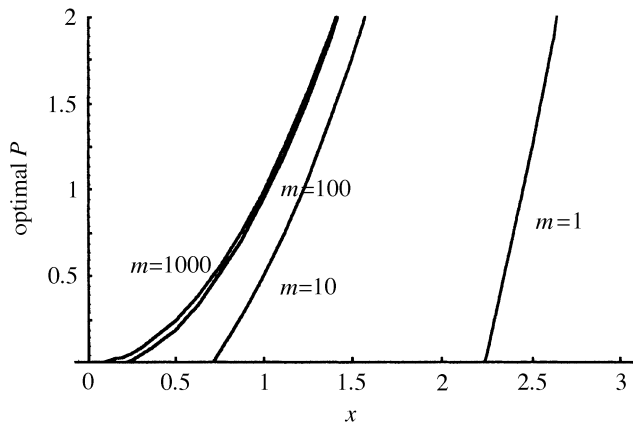


Figure 2. The optimal plasticity as a function of the mean phenotype at given memories. As the mean evolves to the peak of the adaptive landscape ($x=0$), the optimal plasticity decreases according to equation (7). Memory increases the optimal plasticity, and enables the epigenetic inheritance system to be present in the vicinity of the peak. We find remarkable differences between the evolution of plasticity at $m=1$ and $m=10$, due to the drastic increase of the strength of phenotypic selection, but the difference between $m=100$ and $m=1000$ is negligible under given selection intensity. Data: $V_S=5.0$, $\delta_\xi^2=1.0$.

As the intensity of selection or memory increases, this point gets closer to the peak of the landscape. In the case of plastic strategy ($m=1$), the critical point coincides with the inflection point of the landscape ($x_{\text{crit}} = \pm\sqrt{V_S}$). Plasticity is advantageous if the adaptive landscape is convex, and disadvantageous if it is concave. This relationship can also be realized by elementary algebra. I assumed a Gaussian distribution of the phenotypes. Accordingly, any $x-e$, $x+e$ phenotype is generated with the same frequency. It is beneficial to generate $x-e$, $x+e$ phenotypes, instead of the genetically determined x , if the arithmetic mean fitness of the two phenotypes is higher than the fitness of x . Formally, this means

$$W(x) = \frac{W(x-e) + W(x+e)}{2}. \quad (9)$$

By induction, one can easily see that equation (9) is satisfied if, and only if, the fitness function is convex on the given interval (figure 3).

5. GENETIC ASSIMILATION

The exact shape of an arbitrary adaptive landscape can be very complicated, but it is highly probable that it is convex in the beginning, and it tends to become concave closer to a peak. If the character is far from a local optimum, then the generation of phenotypes different from the mean is advantageous. Passing through the critical point of the landscape, selection favours the suppression of phenotypic variation. This is a general description of genetic assimilation, first recognized by Waddington in a population genetic context (Waddington 1953). In the beginning, the optimal phenotype appears with a very low frequency, and is induced by the environment. The frequency of the optimal phenotype increases, as the plasticity increases, and the mean evolves closer to

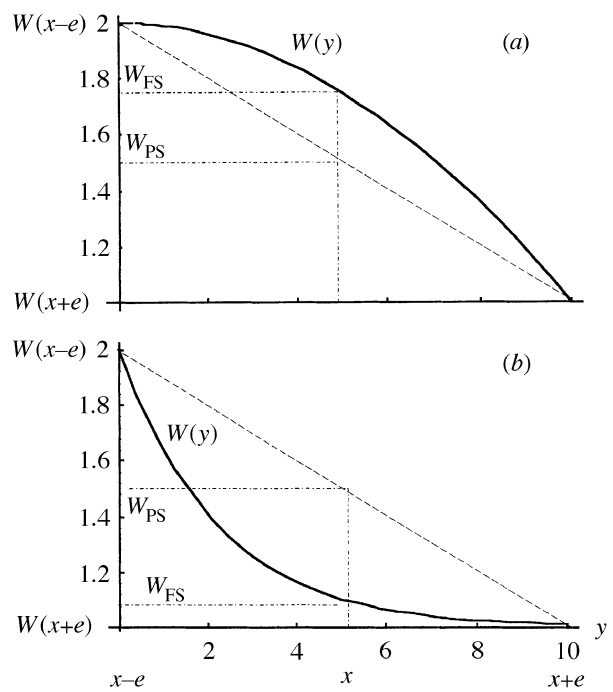


Figure 3. Comparison of the fixed genetic strategy and the strategy with plasticity. If the adaptive landscape— $W(y)$ —is concave on the given interval (a), the arithmetic mean of $W(x-e)$ and $W(x+e)$ is lower than $W(x)$. It means, that in this case the fixed genetic strategy has advantage over the plastic strategy. On the other hand, if the adaptive landscape is convex on the given interval (b), the fitness of the plastic strategy is higher than the fitness of the fixed genetic strategy. Inequality (8) is a special case of the Jensen inequality. Notation: W_{FS} is the fitness of the fixed genetic strategy, W_{PS} is the fitness of the plastic strategy.

the optimal phenotype. Reaching the critical point of the landscape, the suppression of phenotypic variation is selectively advantageous (figure 2). The optimal phenotype, which was originally induced by the environment, becomes genetically ‘fixed’ by the selection acting on the plasticity (P), and the mean (x). Genetic assimilation occurs much closer to the peak if an epigenetic inheritance system is present (equation (8)).

One experiment (Ho *et al.* 1983) showed that the assimilation of the *Bithorax* phenocopy can also occur in inbred lines of *Drosophila*. It was suggested that new epigenetic variants should be responsible for the phenomenon. Jablonka & Lamb (1995) think that these variants can be fixed later by genetic mutations. They proposed that the epigenetic inheritance system has a crucial role in the appearance of novelty, and it can also speed up adaptation.

Last, I would like to quote an example showing how plasticity can play an important role in molecular evolution. Recently, Wedemeyer *et al.* (1997) examined the structure of a catalytic antibody, in both the presence and absence of the binding hapten. They also isolated the corresponding antibody in the germ line. The results of the structural comparisons showed that the antibody from the germ line can reconfigure in the presence of the antigen, and one of the configurations is best able to bind the hapten. This conformation becomes fixed by somatic

mutations in the mature antibody. Plasticity—the possible conformational range of the same antibody—may be a preadaptation for the acquisition of the possible catalytic function (Joyce 1997). In our terminology, it is advantageous to generate phenotypic variation far from the optimum, but it is disadvantageous to do so near to it. The diversity of the germ line repertoire can be greatly expanded if each protein (genotype) can have different conformations (phenotypes).

6. DISCUSSION

The dual inheritance of a character separates the effects of selection on the genotypes and the phenotypes. Under a new selection pressure, a population with low genetic variation seems to be destined to perish. However, the epigenetic inheritance system can produce new heritable variation. The efficiency of phenotypic selection depends on the environmental variance, plasticity and memory.

Phenotypic variation allows for a localized search of the genotype space, which can guide genetic evolution to optima (Hinton & Nowlan 1987; Behera & Nanjundiah 1995). Therefore, epigenetic inheritance systems ensure a brief non-genetic flexibility, but this cannot be the endpoint of adaptation. Rare, advantageous genetic variants of the character can spread in the population. The benefit of phenotypic selection depends on the possibility of finding much better phenotypes than the genetically hard-wired ones. Accordingly, the evolution of the character limits the efficiency of the 'exploratory behaviour' of the epigenetic inheritance systems.

Epigenetic inheritance systems seem to be especially advantageous for organisms in a fluctuating environment (Lachmann & Jablonka 1996). Further improvement of the model can also consider this effect. We have to incorporate into it that the environment acts both as the agent of selection and phenotypic variation, so both the shape of the landscape and microenvironmental variance can change in time and space.

This paper shows that the inheritance of the phenotypes has a temporary effect on the evolution of the character, but it cannot be selectively maintained at the peak of the landscape. In a forthcoming work, I plan to incorporate the effect of mutation and examine the population in mutation–selection equilibria. It can be shown that the dual inheritance of a character is selectively maintained in a constant environment, because it increases the fitness of the suboptimal genotypes.

I am very grateful for the encouragement and criticism of Eörs Szathmáry and Eva Jablonka. The help of János Tóth in preparing the manuscript and clarifying the ideas was also very beneficial.

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