



The Inheritance of Phenotypes: an Adaptation to Fluctuating Environments

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We discuss simple models for the evolution of rates of spontaneous and induced heritable phenotypic variations in a periodically fluctuating environment with a cycle length between two and 100 generations. For the simplest case, the optimal spontaneous transition rate between two states is approximately $1/n$ (where n is the cycle length). It is also shown that selection for the optimal transition rate under these conditions is surprisingly strong. When n is small, this means that the heritable variations are produced by non-classical inheritance systems, including non-DNA inheritance systems. Thus, it is predicted that in genes controlling adaptation to such environments, non-classical genetic effects are likely to be observed. We argue that the evolution of spontaneous and induced heritable transitions played an important role in the evolution of ontogenies of both unicellular and multicellular organisms. The existence of a machinery for producing induced heritable phenotypic variations introduces a “Lamarckian” factor into evolution.

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Introduction

Evolutionary adaptation is usually described as the product of a directional process involving the selection of hereditary variations. The nature and origin of these hereditary variations, and their relationship to the environment in which the organism lives are obviously of fundamental importance for understanding this and other evolutionary processes. It has been customary to assume that the variations are DNA variations, and that their origin is random with respect to the selecting environment. Today both of these assumptions are being questioned. Some variations in DNA, such as phase variations in bacteria, are locus-specific and have very high transition rates between a limited number of locus-specific states (Robertson & Meyer, 1992; Moxon *et al.*, 1994). Moreover, developmentally and environmentally induced changes in DNA sequence

are recognized in both unicellular and multicellular organisms [Volume 8, issue 12, of *Trends in Genetics* 1992 has been devoted to the description of some such systems; see also Schneeberger & Cullis (1991)]. Induced mutations and locus-specific mutation rates are not necessarily adaptive. The role of adaptive mutations in bacteria is at present a hotly debated subject in evolutionary genetics [for opposing views concerning this issue see Foster & Cairns (1992) and Lenski & Mittler (1993)]. However, the existence of non-classical DNA variations such as the high, locus-specific mutation rates found in many pathogenic microorganisms, and the developmentally regulated changes in DNA sequences as, for example, those studied in yeast, raises the problem of the evolution of such systems.

Some heritable variations may not involve a change in DNA sequence (Holliday, 1987; Jablonka & Lamb, 1989; Jablonka *et al.*, 1992). Such heritable variations are normal in complex multicellular organisms, where different cell types are generated from a fertilized egg.

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The various determined states are stable and are transmitted through many cell divisions, in the absence of the stimuli which originally induced the differences. Inheritance systems additional to the system of DNA replication must operate to maintain the stability of these determined states. Epigenetic inheritance systems [abbreviated EIS by Maynard Smith (1990)] are responsible for the inheritance of the functional states of genes and cell structures in cell lineages. Several types of cellular inheritance systems are known: in the *chromatin marking system* chromatin marks such as DNA methylation patterns, or patterns of proteins associated with DNA are carried and transmitted on the chromosomes through cell divisions; in a *steady-state system* inheritance is based on the self-perpetuating properties of reactions involving positive transcriptional self-regulation; in the *structural inheritance system* a three-dimensional structure is used as a template for the same structures in daughter cells [for a discussion of the different systems see Jablonka *et al.* (1992)]. The epigenetic variations may be random with respect to the environment [these were termed epimutations by Holliday (1987)], or they may be induced by the environment. With a chromatin marking EIS, the number of variant heritable states that a locus has is specific to the locus. In both cultured cell lines (Holliday, 1987; Harris, 1989; Meins, 1985) and in unicellular organisms (Jollos, 1921; Nanney, 1960; Pillus & Rine, 1989) hereditary variations which were initially assumed to be classical mutations, were later shown to be epigenetic variations. Inheritance of epigenetic information therefore does occur, and information can be acquired and transmitted in ways that do not involve changes in DNA base sequence.

In addition to genetic and epigenetic inheritance, information can be transmitted via behavioral channels. Social learning, which includes various learning mechanisms, allows transgenerational transmission of behavioral phenotypes in both birds and non-human mammals (Galef, 1988). In humans, cultural evolution is driven by behavioral transmission mediated by language, and is a major factor in the evolution of individual and social behavior [see for example, Cavalli-Sforza & Feldman (1981); Boyd & Richerson (1985)].

The existence of epigenetic variations, transmissible behaviors and non-classical DNA variations, raises the question of the evolution of the inheritance systems underlying them. Under what circumstances is there an advantage in transmitting information acquired by parents to progeny, and how is the fidelity of the transmission related to environmental conditions? Much of the information acquired as a

response to transient environmental stimuli may be irrelevant or deleterious if transmitted to progeny, for it may be caused by factors such as accidents, injuries, and aging. Are there any circumstances in which it is advantageous to inherit a response rather than depending on a renewed response to a stimulus?

The inheritance of a phenotypic response will be advantageous in a changing environment when (a) the environmental conditions which favor this response last longer than the generation time of the organism; (b) there is a lag period before the adaptive response is manifest, and this lag causes a selective stress on the organism. (This could happen either because the stimulus for transition is rare or absent, or because the transition to an active state takes a long time.) Phenotypic transmission can be advantageous under such circumstances, for example when the environment periodically fluctuates.

We shall define a periodically fluctuating environment with a cycle length that is longer than the generation time of the organism, but not long enough to allow adaptation through the fixation of classical mutations, as an Intermediate Length Cycle (ILC) environment. Typical periodic cycles are seasonal fluctuations, diurnal fluctuations, and fluctuations in population density, which may be due to intra-population dynamics, or to interactions between different species such as host-parasite interactions. Organisms that transmit their adaptive functional state to progeny in this type of fluctuating environment will have an advantage. For the progeny of such organisms, some of the cost of being transiently in a non-adaptive state is avoided. It is clear that the periodicity of the environmental fluctuation will determine the evolution of the transition rate from one phenotypic state to another.

In this paper we discuss the evolution of the rate of heritable variations in asexually reproducing organisms, in a periodically fluctuating environment, under non-inducing and inducing conditions. Our basic model is similar to previous models describing the evolution of spontaneous mutation rates (e.g. Kimura, 1967; Levins, 1967; Leigh, 1973; Liberman & Feldman, 1986; Ishii *et al.*, 1989), but we suggest a new interpretation of the model's results for ILC environments, and we describe a model for inducible heritable mutations. We base the interpretation of our models on the properties of transmissible behavior, EISs, and non-classical mutations. The properties of these systems permit the following assumptions: (i) there is a high probability that the transmissible states will be adaptive in specific environmental conditions; (ii) the transition from one state to

another may be either spontaneous or induced by specific stimuli; (iii) the range of rates of transition between variants is expected to be large, varying from a very high rate to a very low rate—comparable to the rate of classical mutations; (iv) the rate of transition (for example, the change in the pattern of methylation of a locus) will be intrinsic to the locus or to the phenotypic state. This latter feature means that it is not necessary to assume the existence of a mutator (or modifier) locus which affects the rate of variation in the whole genome. Consequently, in our model, as in some previous models (for example that of Leigh, 1973; Ishii *et al.*, 1989; Moxon *et al.*, 1994), a high transition rate in one locus or for one phenotype does not increase the genetic load in the population through the accumulation of deleterious variations elsewhere in the genome. The independence of the rate of transition in one locus from the transition rates in other loci means that in our model, an evolutionary stable transition rate for a locus is identical to its optimal transition rate. The models we describe are particularly applicable to the evolution of phase variations in bacteria.

Models and Results

An organism living in a fluctuating environment with a periodicity somewhat longer than its generation time (an ILC situation) could adapt to this environment by passing information about the current state of the environmental conditions to its offspring. We shall first consider the simplest situation, in which the environment does not induce the change in state, but acts only as the selective agent. This is classical Darwinian evolution, with the difference between our model and the conventional one being that for cellular inheritance the information carrier in our model is usually an EIS rather than DNA, and for behavioral inheritance it is the nervous system. The model for phenotypic transmission is described in Fig. 1.

Note that there is no modifier locus which affects the overall transition rate in the genome; the transition rate is local and intrinsic to the locus. The assumptions about the regularity and symmetry of the fluctuating environment simplify the model but can be relaxed without changing its basic results. The model is suitable for a chromatin marking EIS, where information is transmitted as epigenetic marks carried by chromosomal DNA. Variations in chromatin marks are formally most similar to variations in DNA sequences. The model is equally suitable for describing transitions between behavioral phenotypes transmitted by social learning.

With these assumptions the population sizes of A_1 carriers (a_1) and of A_2 carriers (a_2) change every generation. In environment E_1 , in the next generation their new values will be:

$$a'_1 = a_1 w_g (1 - \mu) + a_2 w_b \mu \quad (1)$$

$$a'_2 = a_1 w_g \mu + a_2 w_b (1 - \mu) \quad (2)$$

where a_1, a_2 are the population sizes, μ is the transition rate and w_g, w_b are the fitnesses for the “good” or the “bad” phenotype.

In environment E_2 :

$$a'_1 = a_1 w_b (1 - \mu) + a_2 w_g \mu \quad (3)$$

$$a'_2 = a_1 w_b \mu + a_2 w_g (1 - \mu) \quad (4)$$

thus we have two linear transformations T_1, T_2

$$T_1(\vec{x}) = \mathbf{M}_1 \vec{x} \quad \text{and} \quad T_2(\vec{x}) = \mathbf{M}_2 \vec{x}$$

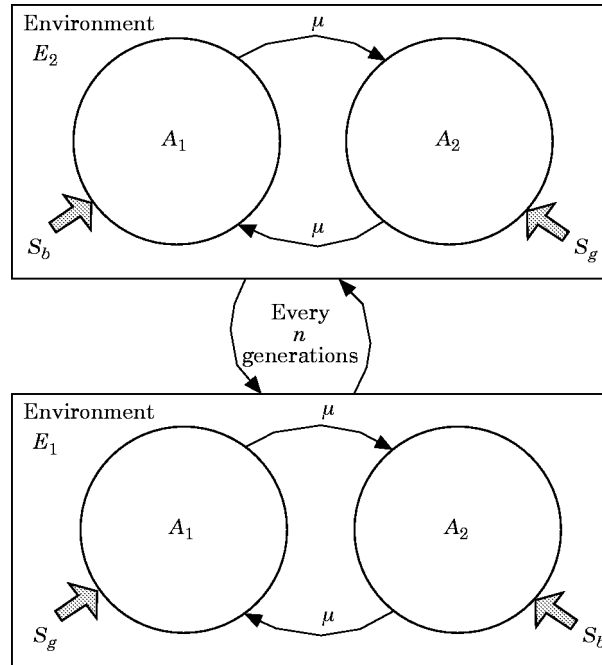


FIG. 1. A simple model for phenotypic transmission in a fluctuating environment, μ is the transition rate, w_b and w_g are the fitnesses in the “bad” and “good” conditions respectively. A_1 and A_2 represent the alternative phenotypes. The model makes the following assumptions: (1) There are two epigenetic phenotypes, A_1 and A_2 , and two states of the environment, E_1 and E_2 . State A_1 is relatively more advantageous in E_1 , and A_2 in E_2 . (2) The environment changes periodically and regularly from state E_1 to state E_2 or vice versa every n generations. (3) The transition coefficient (or epimutation rate) μ is the same in both directions. (4) The “good” and “bad” fitnesses, w_g and w_b , are identical in the two environments.

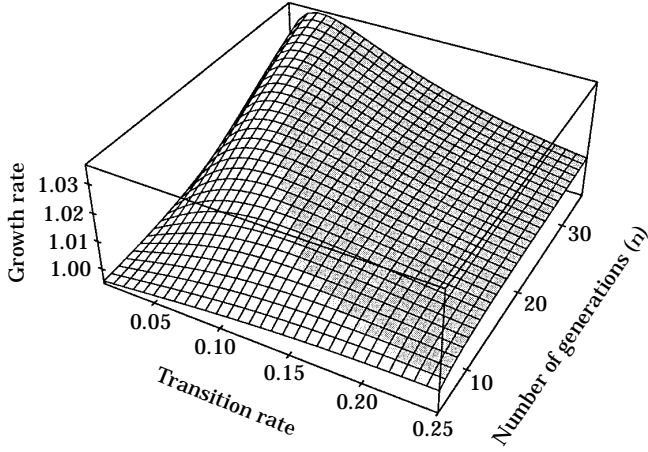


FIG. 2. The population growth per generation for different transition rates and number of generations per fluctuation. w_g and w_b are 1.1 and 0.9 respectively. (To emphasize the maximum, the points on the left of the maximum are lighter than those to the right.)

where \hat{x} is $(a_1, a_2)^T$, and

$$\mathbf{M}_1 = \begin{pmatrix} 1 - \mu & \mu \\ \mu & 1 - \mu \end{pmatrix} \begin{pmatrix} w_g & 0 \\ 0 & w_b \end{pmatrix}, \quad (5)$$

$$\mathbf{M}_2 = \begin{pmatrix} 1 - \mu & \mu \\ \mu & 1 - \mu \end{pmatrix} \begin{pmatrix} w_b & 0 \\ 0 & w_g \end{pmatrix}. \quad (6)$$

The transformation for a whole cycle will be

$$T = \mathbf{M}_2^n \mathbf{M}_1^n$$

where $2n$ is the number of generations in one cycle. The population growth rate for a phenotype with transition rate μ will be the maximal eigenvalue of the transformation. This will be the growth rate for $2n$ generations. The growth rate per generation will be the $2n$ -th root of this (see also Leigh, 1970; Ishii *et al.*, 1989). Figure 2 shows the growth rate per generation plotted against n , the number of generations, and μ , the transition rate. It shows, for example, that for $n = 27$, $w_g = 1.1$ and $w_b = 0.9$, there will be a growth rate of 1.03 for types with $\mu = 0.05$, and 0.99 for types with $\mu = 0.001$. In this case the selection for the optimal transition rate is quite high (4%). Appendix B shows that this result is general. For large enough n , selection for the optimal transition rate is of the order of \sqrt{s} (s is the selection coefficient).

As can be seen in Fig. 2, for each n there is a transition rate μ_{best} which is selectively the most favorable. Figure 3 shows an example: a graph of n vs. μ_{best} (the best transition rate), when w_g and w_b are again 1.1 and 0.9. One can see that for small n , the best transition rate is very high compared with

classical mutation rates (that are in the range of 10^{-4} – 10^{-12}). In cases of asymmetric environmental fluctuations between E_1 and E_2 (n is different in each environment) the best transition rates will not be equal in both directions. The basic result, however, is unchanged: μ_{best} for each environment will still be approximately equal to $1/n$ (see Appendix A).

So far we have described the simplest situation, in which the transition from one state to another is insensitive to environmental induction. The optimum transition rate depends on the length of the fluctuation cycle and on the selection coefficients. Clearly, another option to cope with a fluctuating environment is to adapt to it phenotypically in every generation without transmission to the offspring. However, if the phenotypic change is not instantaneous, there will still be some time in which the organism is not adapted, so there will be a selection pressure towards an optimal transition rate.

Another option, which is adopted by organisms that can learn, in the cell lineages of multicellular organisms, and also in some unicellular organisms, is to have induced transitions. The environment will then enhance transitions from the “bad” to the “good” phenotype. We shall denote the probability for such an induction as v . It is clear that the closer v is to 1 the better. An organism will always benefit from making the transition as fast as possible. To describe this model we used the following matrices (in this model it is assumed there are no random transitions):

$$\mathbf{M}_1 = \begin{pmatrix} 1 & v \\ 0 & 1 - v \end{pmatrix} \begin{pmatrix} w_g & 0 \\ 0 & w_b \end{pmatrix} \quad (7)$$

$$\mathbf{M}_2 = \begin{pmatrix} 1 - v & 0 \\ v & 1 \end{pmatrix} \begin{pmatrix} w_b & 0 \\ 0 & w_g \end{pmatrix} \quad (8)$$

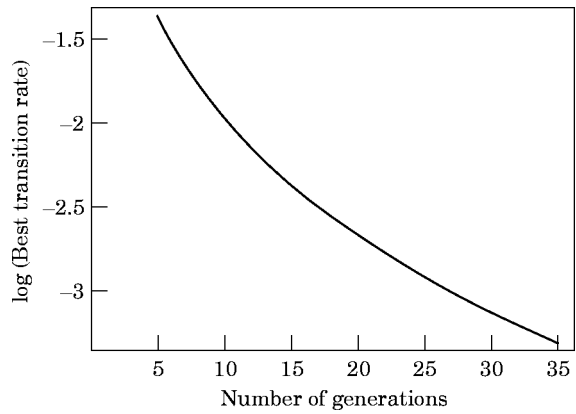


FIG. 3. The best transition-rate for every cycle length. The graph shows log of the transition rate against the number of generations in one cycle. Based on the same simulation as in Fig. 2, with $w_g = 1.1$, $w_b = 0.9$.

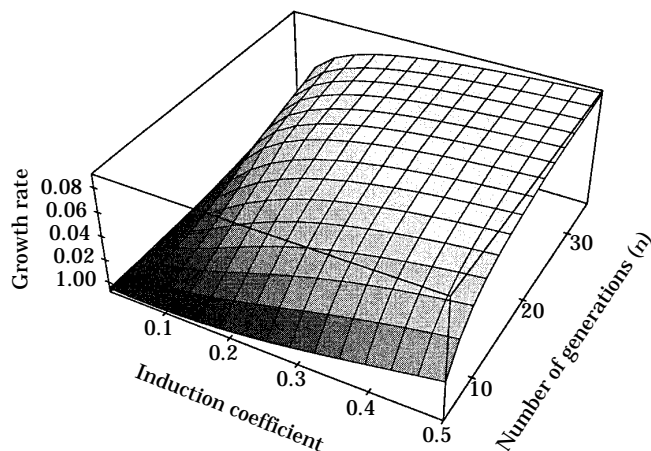


FIG. 4. Population growth per generation for different induction coefficients for different n , the number of generations per fluctuation.

with the transformation for the whole cycle again being $T = \mathbf{M}_2^* \mathbf{M}_1^*$. The growth rate under inducing conditions has been explored by Jablonka *et al.* (1995).

Figure 4 is a graph of the change in the growth rate plotted against n and v (the induced transition rate). To describe induced variation, an induction coefficient is included in the matrices describing the basic model. For each mutation rate μ there is a corresponding induced transition rate v , which causes the same population growth for a given cycle-length. Figure 5 shows, for $n = 20$ and fitnesses 0.9 and 1.1, the values of μ and v that result in the same rate of population growth.

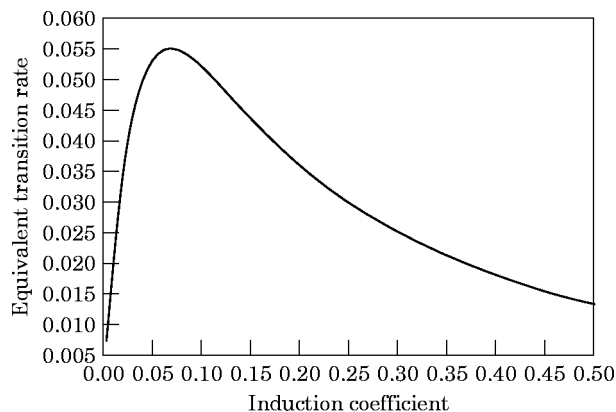


FIG. 5. The relationship between the transition rate, μ , and the induced transition rate v which for constant n , w_g and w_b give rise to the same population growth. It can be seen that in these conditions the best transition rate can achieve only the same population growth as an induced transition rate of $v = 0.055$.

Discussion

Our models show that a locus will have an advantage if it has an intrinsic transition rate corresponding to the environmental periodicity relevant for this locus. It is clear that an ILC environment would pose a problem if organisms only had a general, genome-wide variation rate. In an ILC environment, an organism which has “locus-specific responses and memory systems” will have an obvious advantage. It is important to note that the type of response that is adaptive in an ILC environment is neither facultative (short-term stimulus-dependent response), nor constitutive (long-term, stimulus-independent response) but intermediate between these two; it is an intermediate-term response: a response which can be inherited for a while in the absence of the environmental trigger, but not for a very long period. Such a response can be based on a spontaneous, intrinsic transition rate, on induced transition, or on even more complex learning systems such as with heritable learnt behavioral phenotypes. The results of the basic model we have developed, which are illustrated in Figs 1 and 3, show that the relationship between the rate of a spontaneous transition and the periodicity cycle is $\mu \simeq 1/n$ (see Appendix A). This agrees with the results obtained by Leigh (1970). In our basic model, which describes a typical neo-Darwinian evolutionary system, the environment is merely the selective agent; the hereditary variations can be either variations in DNA, epigenetic variations, or behavioral variations. If we know the duration of the environmental cycle for an organism living in an ILC environment we can predict the corresponding optimal μ . For “small” n ($n < 10^4$) a corresponding high μ will often be found, and indicate that the inheritance system underlying the transitions is an interesting non-classical inheritance system, involving either DNA phase variations, EISs, or transmissible behaviors. We therefore predict that the identification of ILC ecological conditions will often lead to the discovery of unusual heredity systems, and that the identification of genes that behave in a non-classical manner, like genes showing very high mutation rates, may facilitate the identification of the relevant ILC ecological conditions that select for them. Another prediction is that experimental altering of the periodicity of an identified ILC environment would result in selection for correspondingly changed variation rates (or changed induction coefficients, if the trait is environmentally induced) in the relevant hereditary or developmental system.

ILC environments often result from interaction between parasites and hosts, and it is therefore not

surprising that most phase variations, both those involving DNA variations and those involving EISs, have been described in pathogenic microorganisms. In most cases of which we are aware, n is several times greater than the generation time, but not orders of magnitude greater. Some periodic, intermediate-term, heritable, phenotypic transitions may be the result of EISs affecting gene transcription. In uropathogenic *Escherichia coli*, the phase variation in the expression of pili protein is under methylation control. The switching between the “on” and the “off” states depends on the methylation pattern of two GATC sites in the gene’s regulatory region (Nou *et al.*, 1993). Phase transition involving an EIS is also thought to be involved in the infectious yeast *Candida albicans*, which can switch between several alternative phenotypes, and form colonies with alternative characteristic forms. One of the best studied types of switching is between white and opaque. This transition involves a dramatic change in the cellular phenotype, which is reflected in the colony’s morphology and color. The frequency of switching from white to opaque occurs less frequently than in the opposite direction, and the rate of switching is affected by environmental factors. The mechanism of switching is not clear, but it seems to involve an EIS (the chromatin marking EIS) rather than a DNA sequence change (Soll, *et al.*, 1993). It is likely that as with other parasites, *C. albicans* switching has evolved as a response to the changing environment presented by the host’s defense systems. There are many examples of phase variations in pathogenic bacteria that involve DNA changes brought about by various mechanisms such as recombination, gene conversion, slippage, etc. (Robertson & Meyer, 1992). As Moxon *et al.* (1994) have recently argued, phase variations in pathogenic bacteria are an adaptation to the unpredictable environment within the host, with the genes that have products directly interacting with the host (“contingency genes”) evolving very high mutation rates.

The results of Appendix B, showing that the selection pressure for optimal mutation rates in a fluctuating environment is very high (\sqrt{s}), which means that strong forces facilitate the evolution of high, locus-specific hereditary variations. We would therefore expect the evolution of such systems to be very common. The existence of several types of different inheritance systems also facilitates the precise modulation of transition rates. A particular inheritance system may be more suitable than others as a response and heredity system, because it has pre-adaptations allowing more easy adjustment of the relevant phenotypic transition rates in a given environment. The selection of transition rates

between phenotypic states may underlie heritable phenotypic changes in the life-history of organisms that experience ILC environments, including parasites that exploit several different hosts sequentially, organisms with seasonal polyphenisms, and phenomena such as phase variations in plants (Brink, 1962). Phenotypic, behavioral inheritance occurs in organisms exhibiting social learning, and ILC environments may have been an important factor in the evolution of transmitted, socially-learned behavior (Plotkin & Odling Smee, 1979).

The sensitivity of EISs to environmental stimuli, and the rapid switch which may occur from one epigenetic state to another, make the EISs effective cellular response systems as well as effective cellular memory systems. As Fig. 5 shows, environmentally induced variations are more effective than “random” variations, and “random” variations behave as induced variations with a small induction coefficient. Adaptation occurs by accumulating information about the environment and transmitting this information to progeny. The environment is both the inducer of heritable variations and the selective agent. The induction by the environment may be complex and involve several stages. The important point is that the induced state can be transmitted to the offspring; both variations in DNA sequence and epigenetic variations can be induced and transmitted, but epigenetic variations are probably more common, because the environment directly modifies the epigenetic system. In the DNA system, the modified epigenetic state must somehow be transferred to the relevant DNA sequence. This seems to be a more demanding task, although examples of developmentally regulated changes in DNA are not as rare as once believed [for reviews see Watson *et al.* (1987) and vol. 8 issue 12 of Trends in Genetics 1992].

We have argued that in an ILC environment, unicellular organisms can evolve locus-specific transition rates. Locus-specific transitions which are tissue- and stage-specific are also fundamental to the ontogeny of multicellular organisms. The evolution of EISs in unicellular organisms was probably crucial to the evolution of multicellular organisms with complex development, since EISs maintain the determined state of cell lineages. Induced heritable transitions are important in all developing organisms; random transitions may also be important in organisms with regulative development, since in such organisms, they may cause phenotypic heterogeneity which may be the basis for somatic selection (Sachs, 1988).

Adaptation involving heritable induced variations directly links the process of physiological adjustment, which is a process at the level of the individual, with

that of evolutionary adaptation, which is a process at the level of the population. Such a direct link implies a type of “Lamarckian” inheritance. The properties of the epigenetic inheritance systems and of the behavioral transmission systems, and the nature of the periodical fluctuations to which many types of organisms are subjected, determine random and induced heritable phenotypic transition rates. The existence of heritable phenotypic variations, and the way in which the environment influences the transition from one state to another, requires a re-consideration of “Lamarckian” inheritance, not only in the context of ontogeny, but in phylogeny as well.

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APPENDIX A

In this appendix it will be shown that for the first model discussed, μ_{best} under certain assumptions is approximately $1/n$. The transformation for the whole cycle is $T = \mathbf{M}_1^n \mathbf{M}_2^n$ with

$$\mathbf{M}_1 = w_g \begin{pmatrix} 1 - \mu & \mu s \\ \mu & (1 - \mu)s \end{pmatrix}$$

$$\mathbf{M}_2 = w_g \begin{pmatrix} (1 - \mu)s & \mu \\ \mu s & (1 - \mu) \end{pmatrix}. \quad (\text{A.1})$$

s is the selection coefficient, w_b/w_g . For simplicity we assume here that $w_g = 1$. We will assume that n is sufficiently large, so that $n^2 s^n \ll 1$. To compute \mathbf{M}_1^n we will write

$$\mathbf{M}_1^n = \left((1 - \mu) \begin{pmatrix} 1 & 0 \\ 0 & s \end{pmatrix} + \mu \begin{pmatrix} 0 & s \\ 1 & 0 \end{pmatrix} \right)^n$$

$$\equiv ((1 - \mu)A + \mu B)^n \quad (\text{A.2})$$

Using the binomial expansion this gives

$$(1 - \mu)^n A^n + \mu(1 - \mu)^{n-1} \left[\sum_{i=0}^{n-1} A^i B A^{n-i-1} \right] \\ + \mu^2(1 - \mu)^2 \sum_{i_1=0}^{n-2} \sum_{i_2=0}^{n-2} A^{i_1} B A^{i_2} B A^{n-i_1-i_2-2} + \dots \quad (\text{A.3})$$

The general term in this expansion is

$$\mu^l (1 - \mu)^{n-l} \sum_{i_1+i_2+i_3+\dots+i_{l+1}=n-l} A^{i_1} B A^{i_2} B A^{i_3} B \dots B A^{i_{l+1}} \quad (\text{A.4})$$

it can be shown that for $l = 2k$

$$A^{i_1} B A^{i_2} B A^{i_3} B \dots B A^{i_{2k+1}} \\ = \begin{pmatrix} s^{i_2+i_4+i_6+\dots+i_{2k}} & 0 \\ 0 & s^{i_1+i_3+i_5+\dots+i_{2k+1}+k} \end{pmatrix} \quad (\text{A.5})$$

and for $l = 2k + 1$

$$A^{i_1} B A^{i_2} B A^{i_3} B \dots B A^{i_{2k+2}} \\ = \begin{pmatrix} 0 & s^{i_2+i_4+i_6+\dots+i_{2k+1}+k+1} \\ s^{i_1+i_3+i_5+\dots+i_{2k}+k} & 0 \end{pmatrix} \quad (\text{A.6})$$

looking at these terms it is apparent that \mathbf{M}_1^n will have the form

$$\begin{pmatrix} a & sb \\ b & c \end{pmatrix} \quad (\text{A.7})$$

Where a , b , and c are functions of s , μ , and n . And \mathbf{M}_2^n will then be

$$\begin{pmatrix} c & b \\ sb & a \end{pmatrix} \quad (\text{A.8})$$

We wish to compute the eigenvalues of $\mathbf{M}_1^n \mathbf{M}_2^n$. This can be done using the determinant and the trace of the matrix. We know that

$$\det(\mathbf{M}_1^n \mathbf{M}_2^n) = (\det(\mathbf{M}_1))^2 \quad (\text{A.9})$$

(because $\det(\mathbf{M}_1) = \det(\mathbf{M}_2)$), and

$$\det \begin{pmatrix} a & sb \\ b & c \end{pmatrix} = ac - sb^2 = (\det(\mathbf{M}_1))^n \quad (\text{A.10})$$

also

$$\mathbf{M}_1^n \mathbf{M}_2^n = \begin{pmatrix} a & sb \\ b & c \end{pmatrix} \begin{pmatrix} c & b \\ sb & a \end{pmatrix} \\ = \begin{pmatrix} ac + s^2 b^2 & ab(s+1) \\ bc(s+1) & b^2 + ac \end{pmatrix} \quad (\text{A.11})$$

Therefore

$$\text{tr}(\mathbf{M}_1^n \mathbf{M}_2^n) = 2ac + b^2(s^2 + 1) \\ = 2(\det(\mathbf{M}_1))^n + b^2(s+1)^2.$$

So to compute the eigenvalues of $\mathbf{M}_1^n \mathbf{M}_2^n$ it is enough to know b . To find the eigenvalues we have solve the equation

$$\lambda^2 - \lambda(\text{tr}(\mathbf{M}_1^n \mathbf{M}_2^n)) + \det(\mathbf{M}_1^n \mathbf{M}_2^n) = 0 \quad (\text{A.12})$$

or

$$\lambda^2 - \lambda(2(\det(\mathbf{M}_1))^n + b^2(s+1)^2) \\ + (\det(\mathbf{M}_1))^{2n} = 0. \quad (\text{A.13})$$

The maximal eigenvalue is

$$\lambda = (\det(\mathbf{M}_1))^n + \frac{1}{2} b^2(s+1)^2 \\ + \frac{1}{2} b(s+1) \sqrt{2(\det(\mathbf{M}_1))^n + b^2(s+1)^2} \quad (\text{A.14})$$

$$= (\det(\mathbf{M}_1))^n \\ + \frac{1}{2} b^2(s+1)^2 \left(1 + \sqrt{1 + \frac{4(\det(\mathbf{M}_1))^n}{b^2(s+1)^2}} \right) \quad (\text{A.15})$$

The Taylor series expansion $\sqrt{1+x} = 1 + \frac{x}{2} + o[x^2]$ gives

$$\lambda = 2(\det(\mathbf{M}_1))^n + b^2(s+1)^2 \\ + o \left[\left(\frac{4(\det(\mathbf{M}_1))^n}{b^2(s+1)^2} \right)^2 \right]. \quad (\text{A.16})$$

We now turn to compute b . The bound

$$\sum_{i_1+i_2+i_3+\dots+i_{l+1}=n-l} s^{i_2+i_4+i_6+\dots+i_{l+1}+k+1} \\ < \sum_{i_1=0}^{n-l} \sum_{i_2=0}^{n-l} s^{i_2} \sum_{i_3=0}^{n-l} \sum_{i_4=0}^{n-l} s^{i_4} \dots \sum_{i_{l-1}=0}^{n-l} \sum_{i_l=0}^{n-l} s^{i_l} \\ < (n-l)^k \left(\frac{1}{1-s} \right)^{k+1}. \quad (\text{A.17})$$

For $l = 2k + 1$ gives, using eqn (A.6), the following expression for b :

$$b = \sum_{k=0}^{n/2} \mu^{2k+1} (1-\mu)^{n-2k-1} n^k C_k \quad (\text{A.18})$$

where C_k is a function of n and s , decreasing in k . This can be written as

$$b = \mu(1-\mu)^{n-1} C_1 + \mu^3(1-\mu)^{n-3} n C_2 + n^2 o[\mu^5]. \quad (\text{A.19})$$

When we use this expression for $\mu \sim 1/n$, and using our assumption that $n^2 s^n \ll 1$, we see that we can drop the last term in eqn (A.16). To find the μ with the maximal eigenvalue, we will take the derivative of eqn (A.16).

$$\begin{aligned} \frac{d\lambda}{d\mu} = & -4ns^n(1-2\mu)^{n-1} + 2bb' = 2b[(1-n\mu) \\ & \times C_1(1-\mu)^{n-2} + (3-n\mu)C_2n\mu^2(1-\mu)^{n-2} \\ & + n^2 o[\mu^4]] - 4ns^n(1-2\mu)^{n-1} \end{aligned} \quad (\text{A.20})$$

For sufficiently large n the sign of the above expression, for a constant ε , above $(1+\varepsilon)/n$ and below $(1-\varepsilon)/n$ is governed by the term $2b(1-n\mu)C_1(1-\mu)^{n-2}$, and is negative at $(1+\varepsilon)/n$, and positive at $(1-\varepsilon)/n$, which shows that a root exists between these two, or that a maximal eigenvalue is reached there. Thus $1/n$ is a good approximation to μ_{best} .

APPENDIX B

Here we will calculate the fitness advantage of a genotype with mutation rate $1/n$ over a genotype with a very low (or 0) mutation rate. Under the assumptions of Appendix A, it is clear that the growth rate for a whole cycle of $2n$ generations will be s^n for a mutation rate $\mu = 0$. To calculate the selection for $\mu = 1/n$ we use eqn (A.14). This gives us

$$\lambda > \frac{1}{2} b^2 (s+1)^2 \quad (\text{B.1})$$

$$> \frac{1}{2} \mu^2 (1-\mu)^{2n-2} \left(\frac{1-s^n}{1-s} \right)^2 (s+1)^2, \quad (\text{B.2})$$

where we used

$$b > \mu(1-\mu)^{n-1} \left(\frac{1-s^n}{1-s} \right).$$

For big enough n , when $s^n \ll 1$, and $\mu = 1/n$ this gives:

$$\lambda > \frac{1}{2} \left(\frac{1+s}{1-s} \right)^2 e^{-2} \frac{1}{(n-1)^2}. \quad (\text{B.3})$$

Which means that the growth rate is of the form $K(s)n^{-2}$, K is a function which depends only on s , and not on n . If we compare this with the growth rate of s^n for a mutation rate of 0, we see that the relative growth rate of a genotype with $\mu = 1/n$ vs. a genotype with $\mu = 0$ will be $K(s)n^{-2}s^{-n}$ for $2n$ generations, or $(K(s)n^{-2})^{1/2n} 1/\sqrt{s}$ per generation. When n is large enough, this gives $1/\sqrt{s}$. Thus the selection in favor of the ‘‘right’’ mutation rate will be at least of strength \sqrt{s} .