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The Dynamics of Linkage Disequilibrium under Temporal Environmental Fluctuations: Two-Locus Selection

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In this paper, we describe some regularities of the behavior of linkage disequilibrium, D, under temporal environmental fluctuations in infinite panmictic populations with non-overlapping generations and diploid and haploid selecton regimes. Different types of environmental variation ware considered. Our analysis shows that under two-locus haploid selection with any period length, there exists an environmental state (e.s.) where D can change the sign (between periods), but not more than once. The direction of this change is fully determined by a special quantity, "integral fitness disequilibrium coefficient," Δ, which is calculated from genotypic fitness in environmental states. If $\Delta = 0$, then two e.s. exist with only one change of the sign in each. Special types of environments (sub- or super-multiplicative) common in theoretical modelling can be mentioned where the sign of D between periods behaves rather simply for any considered e.s. It can be shown that under sufficiently small rates of recombination $r < r*$ for any period length p in every e.s. the sign of D can change no more than once; the border $r*$ is calculated as a function of fitness values which decreases with decreased differences between the fitnesses. The obtained results were applied to various types of fitness functions. Thus, cases of additive effects of fitness loci on the selected trait under various hypotheses about the selection regime in changing environment were considered in detail. In particular, we showed that the sign of D generated by selection is, in a sense, a nonsymmetrical function when one considers possible forms of fitness dependence on the selected trait: negative D's are more probable. These results are also extended to the diploid case with an additively formed selected trait.

I. INTRODUCTION

Linkage disequilibrium is one of the key notions in population genetics. Analysis of behavior of linkage disequilibrium coefficients (D) is a necessary step in the study of different problems including the nature of stable polymorphic equilibria (Karlin, 1975; Karlin and Feldman, 1978;

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Lewontin 1974), discriminating factors reponsible for the observed patterns of variation in real populations (Thomson and Klitz, 1987; Robinson *et al.*, 1991), evolution of sex and recombination (Feldman *et al.*, 1980; Kondrashov, 1984; Felsenstein, 1988, Maynard Smith, 1988a, b; Charlesworth, 1990), etc. For example, the dynamics of the sign of D is considered to be a crucial factor determining the fate of recombination modifiers in apopulation (Felsenstein, 1988; Charlesworth, 1993).

In this paper we describe some regularities of the behavior of the sign D under environmental fluctuations in infinite panmictic populations with non-overlapping generations. Both diploid and haploid selection regimes were considered. The latter is of special importance providing the possibility of analyzing factors not related to heterozygote advantage.

II. HAPLOID SELECTION

Description of the Model

The dynamics of a two-locus diallelic system with panmixia under haploid selection can be described by the evolutionary operator

$$\begin{aligned} x_1' &= \lambda_{i1}(x_1 - rD)/W_i, & x_2' &= \lambda_{i2}(x_2 + rD)/W_i, \\ x_3' &= \lambda_{i3}(x_3 + rD)/W_i, & x_4' &= \lambda_{i4}(x_4 - rD)/W_i, \end{aligned} \tag{1}$$

which transforms the standard simplex Σ of the four-dimensional space of the genotype frequencies into itself. Here, λ_{ih} is the fitness of haplotype number h ($h = 1, 2, 3, 4$) in the ith environmental state ($1 \leqslant i \leqslant p$), x and x' are the haplotype frequencies in two consecutive generations, r is the recombination rate between selected loci, $D = x_1 x_4 - x_2 x_3$ is the coefficient of linkage disequilibrium, $W_i = \lambda_{i1} x_1 + \lambda_{i2} x_2 + \lambda_{i3} x_3 + \lambda_{i4} x_4 + rD\sigma_i$ is the population mean fitness, and $\sigma_i = \lambda_{i2} + \lambda_{i3} - \lambda_{i1} - \lambda_{i4}$.

Let the geometric mean fitness of the genotype h form generations i to j ($j \geqslant i$) in the power $s = j - i + 1$ be:

$$\begin{aligned} &A_h^{j|i} = \lambda_{ih}, && \text{if } j = i, \\ &A_h^{j|i} = \lambda_{ih} \lambda_{i+1,h} \cdots \lambda_{jh}, && \text{if } j > i \qquad (h = 1, 2, 3, 4). \end{aligned}$$

For a periodic environment ($p < \infty$), if $j = i + p - 1$, then the quantity $A_h^{(i+p-1)|i}$ is the product of fitnesses across the period:

$$A_h^{(i+p-1)|i} = A_h = \lambda_{1h} \lambda_{2h} \cdots \lambda_{ph} \qquad (h = 1, 2, 3, 4).$$

The quantity $A_h^{(i+p-1)|i}$ will be referred to as the integral fitness.

Clearly, $\lambda_{i4}\lambda_{i4}$ and $\lambda_{i2}\lambda_{i3}$ characterize fitnesses of "complementary" pairs of genotypes and, as will be shown below, their proportions affect the behavior of the sign of D along trajectories. For this, we consider the quantity $\delta_i = \lambda_{i1}\lambda_{i4} - \lambda_{i2}\lambda_{i3}$, which, by analogy, could be referred to as the coefficient of fitness disequilibrium. Analogously, we define also the coefficient of integral fitness disequilibrium over the period as $\Delta = \Lambda_1 \Lambda_4 - \Lambda_2 \Lambda_3$ and in the general case, $j\,|\,i$-fitness disequilibrium as

$$\Delta^{j|i} = \Lambda_1^{j|i} \Lambda_4^{j|i} - \Lambda_2^{j|i} \Lambda_3^{j|i}.$$

Note that $\Delta^{(i+p-1)|i} = \Delta$ and $\Delta^{i|i} = \delta_i$ for all $i = 1, 2, ..., p$.

In the case of periodic environments, the states of the population within a period will be enumerated corresponding to the environmental states. Thus, for an arbitrary period, $x^{(i)} = (x_1^{(i)}, x_2^{(i)}, x_3^{(i)}, x_4^{(i)})$ is the set of haplotype frequencies in the environmental state i ($i = 1, ..., p$). The reason for such a designation is that in the further analysis it will be enough to consider only the population changes within a period.

The next statement generalizes for periodic environments a relationship obtained earlier (Eshel and Feldman, 1970; Feldman, 1971) for constant selection regime.

LEMMA 1. *For any ordered pair of environmental states j, i ($j > i$, $j - i < p$), coefficients of linkage disequilibrium $D^{(j)}$ and $D^{(i)}$ corresponding to any two consequent moments within a period obey the relationship*

$$\begin{aligned} D^{(j)} = {} & \Omega_{ji}\, \Delta^{j-1|i} (1-r)^{j-i} x_1^{(i)} x_4^{(i)} + r \sum_{t=i}^{j-1} \Delta^{j-1|t} \Omega_{jt} (1-r)^{j-t-1} C_t \\ & + (1-r)^{j-i} \Lambda_2^{j-1|i} \Lambda_3^{j-1|i} \Omega_{ji}\, D^{(i)}, \end{aligned} \tag{2}$$

where

$$\Omega_{jt} = (W_{j-1} W_{j-2} \cdots W_t)^{-2}, \qquad C_t = [(1-\tau^{(t)})\, x_1^{(t)} x_4^{(t)} + x_2^{(t)} x_3^{(t)} \tau^{(t)}],$$

$$\tau^{(t)} = x_1^{(t)} + x_4^{(t)} - rD^{(t)},$$

and

$$0 \leqslant \tau^{(t)} \leqslant 1, \qquad \Omega_j,\ C_{jt} \geqslant 0 \qquad (t = i, ..., j-1).$$

This connection could be represented also in the form

$$\begin{aligned} D^{(j)} = {} & \Omega_{ji} (\Delta^{j-1|i} + O(r)\, \Psi_{1ji})\, x_1^{(i)} x_4^{(i)} \\ & + \Omega_{ji} ((1-r)^{j-i} \Lambda_2^{j-1|i} \Lambda_3^{j-1|i} + O(r)\, \Psi_{2ji})\, D^{(i)}, \end{aligned} \tag{2'}$$

where $\Psi_{1ji}\Omega_{ji}$ *and* $\Psi_{2ji}\Omega_{ji}$ *are bounded while the boundary grows with the difference* $j-i<p$. (*For the proof, see Appendix* 1.)

One should mention that in addition to $D^{(i)}$ and $D^{(j)}$, the relationships (2) and (2′) include also haplotype frequencies and linkage disequilibria for all intermediate states between i and j. Thus, these relationships should not be considered as evolutionary equations for D. Nevertheless, these relationships are important for obtaining some further estimates.

The connection between consecutive values of D could also be of interest in attempts to discriminate between selection and hitch-hiking of a neutral locus linked to a selected one (e.g., Asmussen and Clegg, 1981).

For each environmental state i one can consider a sequence $\Delta^{i|i}$, $\Delta^{i|i-2}$, ..., $\Delta^{i|i-p+1}$. We call a state i essentially positive if all elements of this sequence are non-negative and essentially negative if all elements are non-positive.

LEMMA 2. *If integral fitness* Δ *is positive, then at least one essentially positive state exists, while if* $\Delta<0$, *then at least one essentially negative state exists. If* $\Delta=0$, *but at least one state exists with* $\delta\neq 0$, *then both essentially positive and negative states exist. If* $\delta=0$ *for each of the environmental states, then each state is positive and negative simultaneously.* (*For the proof, see Appendix* 2.)

Based on these results, we can now analyze how the coefficients affect the sign of linkage disequilibrium.

PROPOSITION 1. *Let the integral fitness* Δ *be non-zero. Then one can find within the period such an environmental state,* i $(1\leqslant i\leqslant p)$, *that for a finite number of generations the sign of* $D^{(i)}$ *becomes the same as that of* Δ, *and only one change in the sign of* $D^{(i)}$ *is possible along the trajectory. If* $\Delta=0$, *but fitness disequilibrium* δ *is non-zero in at least one of the states, then there exist of environmental states* E_1 *and* E_2 *with no more than one change of* sign(D) *in each of them.* (*The proof of this result can be found in Appendix* 3.)

Thus, with any period length, there exists an environmental state where the behavior of D is, in a sense, rather simple: sign(D) could change (between periods!) no more than once. The direction of this change is fully determined by the integral fitness disequilibrium coefficient Δ, which is calculated from genotype fitnesses across the period. In the other environmental states, the number of changes in the sign of D might be higher and numerous examples of such kinds could easily be found. Based on computer experiments, we can hypothesize that the upper limit of the number of changes in the sign (D) exists and it is equal to the length of the period (p).

We showed above that in any cyclical environment, one can find within the period some environmental states with simple behavior between periods along the trajectory. Below, an interesting and rather general class of environments is considered with simple behavior of D in all states. In accordance with the terminology introduced by Eshel and Feldman (1970), a state i could be referred to as: (a) supermultiplicative, if $\delta_i > 0$; (b) submultiplicative, if $\delta_i < 0$; and (c) multiplicative, if $\delta_i = 0$.

If all p states $(p < \infty)$ belong to one of these three types, we will call such an environment a "concordant environment," and correspondingly, one could recognize three types of concordant environments: supermultiplicative, submultiplicative, and multiplicative.

PROPOSITION 2. *Along any trajectory of the system* (1) *the linkage disequilibrium coefficient D becomes, after some number of generations, non-negative if the environment is supermultiplicative and non-positive if the environment is submultiplicative. The number of generations needed for the stabilization of* sign(D) *depends on the trajectory, but the number of steps is always finite. If the environment is multiplicative, then* sign(D) *remains constant along the trajectory.*

This proposition directly follows from Proposition 1.

Another type of simple behavior of sign(D) can be demonstrated when the recombination rate between loci is small. Namely, the following is true.

PROPOSITION 3. *If the coefficient of integral fitness disequilibrium Δ is non-zero, then with small enough r no more than one-change in the sign of D is possible for each of the environmental states.*

Proof. In order to obtain the connection between D's in the state j in two neighboring periods, let us put $i = j - p$ into (2′):

$$\begin{aligned} D^{(j)} = {} & \Omega_{ji}(\Delta^{j-1|i} + O(r)\,\Psi_{1ji})\,x_1^{(i)}x_4^{(i)} \\ & + \Omega_{ji}((1-r)^{j-i}\,\Lambda_2^{j-1|i}\,\Lambda_3^{j-1|i} + O(r)\,\Psi_{2ji})\,D^{(i)}. \end{aligned}$$

Clearly, with small enough r, the multiplier at $D^{(i)}$ is positive while that at $x_1^{(i)}x_4^{(i)}$ is equal to sign$(\Delta^{j-1|j-p}) =$ sign(Δ). Let sign(Δ) be positive. If $D^{(i)}$ is also positive, then, according to the previous relationship, the value $D^{(i+p)}$ will necessarily be positive also. Thus, we have only two possibilities for the sign dynamics of the sequence $D^{(i)}, D^{(i+p)}, D^{(i+2p)}, \ldots$ which is either always negative or starting from some moment becomes positive and remains positive.

The same consideration could be provided for the case $\Delta < 0$.

The above general statements can be applied to various fitness functions. Consider in more detail situations arising when the fitness values are dependent on a trait controlled by additively acting genes. Then, changes of environmental states can be simply interpreted as temporal changes of the optial (i.e., selected for) value for the trait.

Let the trait under consideration be dependent on allelic content of the selected loci, according to

$$\begin{array}{lcc} & \mathrm{a} & \mathrm{A} \\ \hline \mathrm{b} & m & m+d_{\mathrm{A}} \\ \mathrm{B} & m+d_{\mathrm{B}} & m+d_{\mathrm{A}}+d_{\mathrm{B}}, \end{array} \qquad (3)$$

where d_{A} and d_{B} ($d_{\mathrm{A}}, d_{\mathrm{B}} \geqslant 0$) are the effects of allele substitutions and m is the trait value of genotype ab.

We will define the fitness of a genotype with trait value z at an environmental state i as $F(z - z_i)$, where z_i is the current optimal level of the trait and $F(\cdot)$ is the function transforming the deviation of z from z_i into the fitness. Then we can write

$$\lambda_{i1} = F(m + d_{\mathrm{A}} + d_{\mathrm{B}} + L_i), \qquad \lambda_{i2} = F(m + d_{\mathrm{A}} + L_i),$$

$$\lambda_{i3} = F(m + d_{\mathrm{B}} + L_i), \qquad \lambda_{i4} = F(m + L_i),$$

where L_i defines the shift of the maximum of the fitness function. Clearly, genotypic fitnesses in each of the environmental states depend on the fitness function F and the set $L = (L_1, L_2, ..., L_p)$. If the set L does not change in time, one can speak about a periodical environment.

To simplify the formulae, we denote $x = (2m + d_{\mathrm{A}} + d_{\mathrm{B}})/2$, $m + d_{\mathrm{A}} = x + \varepsilon'$, $m + d_{\mathrm{B}} = x - \varepsilon'$, $m = x - \varepsilon$, $m + d_{\mathrm{A}} + d_{\mathrm{B}} = x + \varepsilon$ ($\varepsilon' \leqslant \varepsilon$). The convenience of these designations is that the members of the pairs $(m + d_{\mathrm{A}}, m + d_{\mathrm{B}})$ and $(m, m + d_{\mathrm{A}} + d_{\mathrm{B}})$ are equally distant from the point x. It should be mentioned that with equal effects of loci A/a and B/b $\varepsilon' = 0$.

In these terms the coefficient of fitness disequilibrium at the environmental state i can be written as

$$\delta_i(F) = F(x + \varepsilon + L_i)\, F(x - \varepsilon + L_i) - F(x + \varepsilon' + L_i)\, F(x' - \varepsilon + L_i). \qquad (4)$$

PROPOSITION 4. *If* log(F) *is convex up* (*convex down*), *then the environment defined by function* F *is submultiplicative* (*supermultiplicative*). *The condition of convexness or concaveness is necessary and sufficient for the environment to be sub- or supermultiplicative under any mode of cyclical changes of the optimum* (*i.e., for any set* $L = (L_1, L_2, ..., L_p)$).

Proof. If $\log(F)$ is a convex up function then for any values of x, ε, ε' $(\varepsilon' \leqslant \varepsilon)$, the following inequality holds:

$$\begin{aligned}&\log(F(x+\varepsilon+L_i))+\log(F(x-\varepsilon+L_i))\\&\qquad\leqslant \log(F(x+\varepsilon'+L_i))+\log(F(x-\varepsilon'+L_i))\end{aligned} \tag{5}$$

(see, e.g., Hardy, 1922). Thus

$$F(x+\varepsilon+L_i)\,F(x-\varepsilon+L_i)\leqslant F(x+\varepsilon'+L_i)\,F(x-\varepsilon'+L_i). \tag{6}$$

Therefore, $\delta_i(F)\leqslant 0$. On the other hand, if for all x, ε, ε' $(\varepsilon'\leqslant\varepsilon)$, the inequality (5) is true, then $\log(F)$ is convex up. This follows, from example, from the standard definition of a convex up function,

$$\log(F(x+\varepsilon+L_i))+\log(F(x-\varepsilon+L_i))\leqslant 2\log(F(x+L_i)),$$

resulting from (5) when $\varepsilon'=0$.

The case of convex down $\log(F)$ can be considered in the same manner.

III. Diploid Selection

The evolutionary operator in this case can be written as

$$\begin{aligned}x_1'&=(W_1x_1-r\lambda_dD)/W, & x_2'&=(W_2x_2+r\lambda_dD)/W,\\ x_3'&=(W_3x_3+r\lambda_dD)/W, & x_4'&=(W_4x_4-r\lambda_dD)/W,\end{aligned} \tag{7}$$

where x and x' are haplotype frequencies in two consecutive generations; D, as usual, is the linkage disequilibrium;

$$W_h=\lambda_{h1}x_1+\lambda_{h2}x_2+\lambda_{h3}x_3+\lambda_{h4}x_4, \qquad h=1,2,3,4$$

is the marginal fitness of the haplotype i; the mean fitness of the population is:

$$W=x_1W_1+x_2W_2+x_3W_3+x_4W_4.$$

Coefficient λ_{hj} is the fitness of the zygote (h,j); λ_d denotes the fitness of double heterozygotes (we assume here that $\lambda_d=\lambda_{14}=\lambda_{23}$). As in the previous section, we can calculate the fitness disequilibrium coefficients $\delta=W_1W_4-W_2W_3$ for each of the environmental states.

It should be mentioned here that the evolutionary operators for the haploid (1) and diploid (7) cases use different census-points. This was done only for the sake of technical convenience.

For the following analysis we need a "direct" presentation of δ in the form

$$\delta = \delta' - D(\lambda_{12}\lambda_{43} - \lambda_{32}\lambda_{23}), \tag{8}$$

where

$$\begin{aligned}\delta' = {} & x_1^2(\lambda_{11}\lambda_{41} - \lambda_{21}\lambda_{31}) + x_1x_2(\lambda_{11}\lambda_{42} - \lambda_{31}\lambda_{22}) + x_1x_3(\lambda_{11}\lambda_{43} - \lambda_{21}\lambda_{33}) \\ & + x_1x_4(\lambda_{11}\lambda_{44} - \lambda_{31}\lambda_{24}) + x_2^2(\lambda_{12}\lambda_{42} - \lambda_{32}\lambda_{22}) \\ & + x_2x_3(\lambda_{42}\lambda_{13} - \lambda_{33}\lambda_{22}) + x_2x_4(\lambda_{12}\lambda_{44} - \lambda_{34}\lambda_{22}) \\ & + x_3^2(\lambda_{13}\lambda_{43} - \lambda_{33}\lambda_{23}) + x_3x_4(\lambda_{13}\lambda_{44} - \lambda_{24}\lambda_{33}) \\ & + x_4^2(\lambda_{14}\lambda_{44} - \lambda_{24}\lambda_{34}).\end{aligned}$$

Coefficient $\lambda_{1h}\lambda_{4h} - \lambda_{2h}\lambda_{3h}$ at x_h^2 can be considered as a measure of fitness disequilibrium of progenies resulting from the union of gametes 1, 2, 3, 4 with the gamete h. Let us call $\lambda_{1h}\lambda_{4j} - \lambda_{2h}\lambda_{3j}$ partial coefficients of fitness disequilibrium. Clearly, these quantities are constants, while δ changes over generations according to the changes in genotype frequencies (in contrast to the case of haploid selection, where δ is also constant).

The signs of δ and D are connected in accordance to the following dynamic condition: if $\delta < 0$ and $D > 0$, then the inequality

$$\begin{aligned}\frac{x_1'x_4'}{x_2'x_3'} &= \frac{(W_1x_1 - r\lambda_d D)(W_4x_4 - r\lambda_d D)}{(W_2x_2 + r\lambda_d D)(W_3x_3 + r\lambda_d D)} \\ &= \frac{W_1W_4x_1x_4 - r\lambda_d D(W_1x_1 + W_4x_4 - r\lambda_d D)}{W_2W_3x_2x_3 + r\lambda_d D(W_2x_2 + W_3x_3 + r\lambda_d D)} \\ &< \frac{W_1W_4x_1x_4}{W_2W_3x_2x_3}\end{aligned} \tag{9}$$

is true and D decreases along the trajectory (see also Eshel and Feldman, 1970). An analogous relationship holds when $\delta > 0$ and $D < 0$. Therefore, the population structure tends to change in such a manner that D will become the same sign as that of δ. We should mention that, in contrast to haploid selection, diploid selection regime can result in changes of sign(δ) along trajectory. This coevolution of signs may help us in understanding the mechanisms of diploid selection on corresponding parts of the system trajectories. The permanency of the sign of δ along the trajectory in a constant or variable environment is an important feature which singles out "simple" systems. By analogy to the definition for the haploid case, it is natural to call an environment super- or submultiplicative, depending on the signs of δ.

The variable δ is a quadratic function of genotype frequencies. The sufficient condition for the permanency of its sign follows from the known criterion of Sylvester (Gantmakher, 1960). But this condition is not a necessary one because δ is defined only in the positive octant. We can also formulate a clear necessary condition for the permanency of sign(δ): partial fitness disequilibria $\lambda_{1h}\lambda_{4h} - \lambda_{2h}\lambda_{3h}$ $(h = 1, ..., 4)$ should be of the same sign.

The question of the permanency of the form δ on the simplex Σ can be cleared up by considering the 3-dimensional space containing the simplex S: $x_1 + x_2 + x_3 \leqslant 1$, $x_1, x_2, x_3 \geqslant 0$; the equation $\delta = 0$ defines in this space a conic surface. Clearly, the form δ will be of a permanent sign if this surface has no intersection with the set S. A criterion for such a location of the surface $\delta = 0$ can be obtained but it will be rather cubersome.

For fitness disequilibria of a definite sign, it is easy to derive from (9) the following:

Proposition 5. *Let δ be either a plus-definite or a minus-definite quadratic form. Then, along the trajectory, for a finite number of steps D will achieve the same sign as δ.*

Let us connect now the values of D in two consecutive generations for the case of diploid selection. We have

$$D' = x'_1 x'_4 - x'_2 x'_3 = (W_1 W_4 x_1 x_4 - r\lambda_{23} D(W_1 x_1 + W_4 x_4) + (r\lambda_{23} D)^2$$
$$- W_2 W_3 x_2 x_3 - r\lambda_{23} D(W_2 x_2 + W_3 x_3) - (r\lambda_{23} D)^2)/W^2.$$

Therefore

$$D' = (\delta x_1 x_4 + (W_2 W_3 - r\lambda_{23} W)\, D)/W^2$$

or

$$D' = (\delta x_2 x_3 + (W_1 W_4 - r\lambda_{23} W)\, D)/W^2.$$

From this, it is easy to obtain the connection in a symmetric form

$$D' = (\delta(x_2 x_3 + x_1 x_4) + (W_1 W_4 + W_2 W_3 - 2r\lambda_{23} W)\, D)/(2W^2), \tag{10}$$

and then, with (8), we have finally

$$D' = \{\delta'(x_2 x_3 + x_1 x_4) + \Omega D\}/(2W^2), \tag{11}$$

where

$$\Omega = -(\lambda_{12}\lambda_{43} - \lambda_{32}\lambda_{23})(x_2 x_3 + x_1 x_4) + W_1 W_4 + W_2 W_3 - 2r\lambda_{23} W.$$

After simple transformations, we obtain

$$\begin{aligned}\Omega = {} & x_1^2 \lambda_{21} \lambda_{31} + x_1 x_2(\lambda_{11} \lambda_{42} + \lambda_{31} \lambda_{22}) + x_1 x_3(\lambda_{11} \lambda_{43} + \lambda_{21} \lambda_{33}) \\ & + x_1 x_4(\lambda_{11} \lambda_{44} + \lambda_{31} \lambda_{24}) + x_2^2 \lambda_{12} \lambda_{42} + x_2 x_3(\lambda_{42} \lambda_{13} + \lambda_{22} \lambda_{33}) \\ & + x_2 x_4(\lambda_{12} \lambda_{44} + \lambda_{34} \lambda_{22}) + x_3^2 \lambda_{13} \lambda_{43} + x_3 x_4(\lambda_{13} \lambda_{44} + \lambda_{24} \lambda_{33}) \\ & + x_4^2 \lambda_{24} \lambda_{34} + (1 - 2r) \lambda_{23} W.\end{aligned}$$

Now it is clear that Ω from (11) is non-negative if $r \leqslant 0.5$.

From (11) some conclusions can also be derived about the behavior of sign(D):

PROPOSITION 6. *If in each of the states of a cyclical environment the quadratic forms* δ'_i ($i = 1, 2, ..., p$) *are all positive or all negative and* $r \leqslant 0.5$, *then no more than one change in* sign(D) *is possible in each of the states between periods along the trajectory. This change can occur only if in the initial state* sign(D) sign(δ') $= -1$.

Comment 1. The condition $r \leqslant 0.5$ is biologically justified. However, one can not exclude, in principle, situations with r slightly exceeding the level 0.5 (Carter and Robertson, 1952). Akin has showed that this border value $r = 0.5$ is important also in other situations concerned with behavior of two locus diploid systems (see Lyubich, 1992).

Comment 2. A difference in the situations described by Propositions 5 and 6 should be stressed here. The first proposition tells us that sign(D) after a finite number of steps becomes equal to sign(δ). But generally it remains unknown whether or not the signs differ again in the future. According to the second one, with sign definite form δ', the sign of D can change no more than once, but it is unknown if this change will occur at all.

Comment 3. One could mention that Propositions 5 and 6 are diploid analogs of Proposition 2 concerned with haploid selection regime. However, Propositions 5 and 6 cannot be readily obtained from Proposition 2. Indeed, Proposition 5 is based on inequality (9), which has its haploid analog but still needs to be proved. Moreover, the condition $r \leqslant 0.5$, which appears in Proposition 6, is not important in the haploid case, indicating on (at least technical) difference of the haploid and diploid cases.

These general results will be illustrated by some examples related to selection for an additively controlled trait (x) with unequal effects of the genes under consideration. The fitness of a genotype is described by a function F defined on the trait values x. The dependence of the trait value on genes involved can be set by the table

	aa	Aa	AA
bb	$m-d_A-d_B$	$m-d_B$	$m+d_A-d_B$
Bb	$m-d_A$	m	$m+d_A$
BB	$m-d_A+d_B$	$m+d_B$	$m+d_A+d_B$,

where d_A and d_B are the substitution effects of loci A/a and B/b. Now denote $d_A=d$, $d_B=d+\varepsilon$, $m \geqslant d$, $\varepsilon \geqslant 0$ (the case of equal gene effects corresponds to $\varepsilon=0$). For the sake of simplicity, we assume that the above parameters (m, d_A, and d_B) are constant.

Let $\varepsilon < d$, for definiteness. By ordering the genotypes in accordance with increasing value of the selected trait we obtain

bb	bb	Bb	bb	Bb	BB	Bb	BB	BB
aa	Aa	aa	AA	Aa	aa	AA	Aa	AA

$$m-(2d+\varepsilon) \leqslant m-(d+\varepsilon) \leqslant m-d \leqslant m-\varepsilon \leqslant m \leqslant m+\varepsilon \leqslant m+d \leqslant m+(d+\varepsilon) \leqslant m+(2d+\varepsilon).$$

We have here four pairs of the trait values which are equidistant from the double heterozygote. For simplicity, let $2d+\varepsilon=\varepsilon_1$, $d+\varepsilon=\varepsilon_2$, $d=\varepsilon_3$, $\varepsilon=\varepsilon_4$. Then, the fitness matrix can be written in the form

	AB	Ab	aB	ab
AB	$F(m+\varepsilon_1)$	$F(m+\varepsilon_3)$	$F(m+\varepsilon_2)$	$F(m)$
Ab	$F(m+\varepsilon_3)$	$F(m-\varepsilon_4)$	$F(m)$	$F(m-\varepsilon_2)$
aB	$F(m+\varepsilon_2)$	$F(m)$	$F(m+\varepsilon_4)$	$F(m-\varepsilon_3)$
ab	$F(m)$	$F(m-\varepsilon_2)$	$F(m-\varepsilon_3)$	$F(m-\varepsilon_1)$.

By employing general expressions (8), we can obtain fitness disequilibrium coefficients for this special case,

$$\delta=\delta'-[F(m+\varepsilon_3)\,F(m-\varepsilon_3)-F(m)\,F(m)]\,D,$$

where

$$\begin{aligned}
\delta' &= x_1^2[F(m+\varepsilon_1)\,F(m)-F(m+\varepsilon_2)\,F(m+\varepsilon_3)] \\
&\quad + x_1x_2[F(m+\varepsilon_1)\,F(m-\varepsilon_2)-F(m+\varepsilon_2)\,F(m-\varepsilon_4)] \\
&\quad + x_1x_3[F(m+\varepsilon_1)\,F(m-\varepsilon_3)-F(m+\varepsilon_3)\,F(m+\varepsilon_4)] \\
&\quad + x_1x_4[F(m+\varepsilon_1)\,F(m-\varepsilon_1)-F(m+\varepsilon_2)\,F(m-\varepsilon_2)] \\
&\quad + x_2^2[F(m+\varepsilon_3)\,F(m-\varepsilon_2)-F(m-\varepsilon_4)\,F(m)] \\
&\quad + x_2x_3[F(m+\varepsilon_2)\,F(m-\varepsilon_2)-F(m+\varepsilon_4)\,F(m-\varepsilon_4)]
\end{aligned}$$

$$
\begin{aligned}
&+x_2x_4[F(m+\varepsilon_3)\,F(m-\varepsilon_1)-F(m-\varepsilon_4)\,F(m-\varepsilon_3)]\\
&+x_3^2[F(m+\varepsilon_2)\,F(m-\varepsilon_3)-F(m)\,F(m+\varepsilon_4)]\\
&+x_3x_4[F(m+\varepsilon_2)\,F(m-\varepsilon_1)-F(m+\varepsilon_4)\,F(m-\varepsilon_2)]\\
&+x_4^2[F(m-\varepsilon_1)\,F(m)-F(m-\varepsilon_2)\,F(m-\varepsilon_3)]. \qquad (13)
\end{aligned}
$$

If the function F is logarithmically convex up, then all of the coefficients in (13) are non-positive. Indeed, in these coefficients,

$$
\begin{aligned}
&F(m+\varepsilon_1)\,F(m)-F(m+\varepsilon_2)\,F(m+\varepsilon_3),\\
&F(m+\varepsilon_1)\,F(m-\varepsilon_2)-F(m+\varepsilon_2)\,F(m-\varepsilon_4),\\
&F(m+\varepsilon_1)\,F(m-\varepsilon_3)-F(m+\varepsilon_3)\,F(m+\varepsilon_4),\\
&F(m+\varepsilon_1)\,F(m-\varepsilon_1)-F(m+\varepsilon_2)\,F(m-\varepsilon_2),\\
&F(m+\varepsilon_3)\,F(m-\varepsilon_2)-F(m-\varepsilon_4)\,F(m),\\
&F(m+\varepsilon_2)\,F(m-\varepsilon_2)-F(m+\varepsilon_4)\,F(m-\varepsilon_4),\\
&F(m+\varepsilon_3)\,F(m-\varepsilon_1)-F(m-\varepsilon_4)\,F(m-\varepsilon_3),\\
&F(m+\varepsilon_2)\,F(m-\varepsilon_3)-F(m)\,F(m+\varepsilon_4),\\
&F(m+\varepsilon_2)\,F(m-\varepsilon_1)-F(m+\varepsilon_4)\,F(m-\varepsilon_2),\\
&F(m-\varepsilon_1)\,F(m)-F(m-\varepsilon_2)\,F(m-\varepsilon_3),
\end{aligned}
$$

because of (12) the sums of arguments of the first pairs of multipliers are equal to analogous sums for the second pairs, while the second pairs lie within intervals delimited by elemented of the corresponding first pairs. Therefore, all of them obey the functional relationship

$$\log(F(x+\varepsilon))+\log(F(x-\varepsilon))\leqslant\log(F(x+\varepsilon'))+\log(F(x-\varepsilon')) \qquad (\varepsilon'\leqslant\varepsilon),$$

which is characteristic for a convex up function. For convex down functions $\log(F)$ the coefficients will be non-negative. The above calculations and the Proposition 6 lead to the following statement.

PROPOSITION 7. *With selection for an additively formed trait in an environment with p states ($p<\infty$) linkage disequilibrium D changes the sign no more than once, if the fitness function F is logarithmically convex. The change is possible only from plus to minus if F is* log-*convex up and from minus to plus if F is* log-*convex down.*

IV. DISCUSSION

Understanding the behavior of the sign of linkage disequilibrium is an important tool for studying different aspects of multilocus system dynamics, including polymorphism maintenance and mutation–selection balance, revealing the nature of past evolutionary steps (Thomson and Klitz, 1987), genetic architecture of quantitative traits, evolution of recombination and mating system, etc. Here, we have studied some rather general regularities concerning the question of how temporary variations in selection coefficients affect the sign of linkage disequilibrium along the trajectory of two-locus systems, in both haploid and diploid cases.

For cyclical haploid selection the existence of an environmental state has been shown for which the sign of linkage disequilibrium can be changed from period to period along the trajectory no more than once. The very possibility of this change depends on the sign of a selection parameter "integral fitness disequilibrium." It is clear that this result is a generalization of the corresponding clear fact known for constant selection regime (Eshel and Feldman, 1970; Feldman, 1971). We hope that it could be useful in attempts to construct a two-locus analog of Fisher's theorem (namely, helping to overcome "the initial point effect"). We have also shown that with tight linkage the above property is characteristic for all environmental stages within the period.

In general, the analysis of fitness disequilibrium enables us to discern a class of variable selection systems (namely, the multiplicative systems) with a relatively simple behavior of D along the trajectory (in the sense of Propositions 2 and 6). This approach was used to study the effect of selection for an additively controlled two-locus trait in changing environment on the dynamics of sign(D).

Consider some examples of stabilizing selection defined by some variants of functions $F(x)$ with optimum value of the trait changing cyclically along the period. First, it should be mentioned that for double differentiable F the condition of the convexity (up) of the log(F) (log-convexity) can be written in the form:

$$Q = F'' - F'^2 \leqslant 0. \tag{14}$$

Some qualitative conclusions can be drawn from this condition. The property of a function to be a log-convex defines a more broad class of functions than the convex ones only. Therefore, one could expect that selection against deviations from an optimum will favor negative, rather than positive, linkage disequilibria (e.g., Mather, 1943; Maynard Smith, 1988a, b). Moreover, by replacing, for the sake of simplicity, one F by another, one can in principle replace also the type of F (in the above sense). As a consequence, a qualitatively different dynamics can be obtained. The condition (14) can be considered as a tool to control the possibility of such a transition.

Another point of interest is the estimation of the form of F based on observations on quantitative traits in real populations. Estimation of the intensity of selection in natural populations based on phenotypic traits occupies an important place in the range of evolutionary problems and is still far from being solved, though considerable progress has been made in recent years (Lande and Arnold, 1983; Manly, 1985; Endler, 1986; Mitchell-Olds and Shaw, 1987; Jain, 1990). Especially attractive in this connection seems to be the non-parametric description of fitness surfaces (Schluter, 1988), since it has been shown that the dynamics of multilocus systems that are subjected to selection may strongly depend on the distribution shape adopted (Turelli and Barton, 1990). It is clear that for the same set of data one can suggest rather different (in the sense of criterion (14)), approximations which give, nevertheless, the same statistical precision.

In population genetic models discussed in the literature, we can find a spectrum of various forms of $F(x)$. Application of our criterion shows that most of them lead to negative linkage disequilibria. For example, $F(x) = \exp(-C\,|x-a|^m)$ ($C > 0$, $m = 1, 2, \ldots$) is log-convex up for any set of parameters C, m and a. This property is characteristic also to the family $F(x) = 1 - C\,|x-a|^m$. By contrast, Gillespie's (1976) fitness function $F(x) = c + (1-c)(1+\alpha)\,x/(\alpha+x)$ is log-convex down. Therefore, according to Proposition 7, no more than one change in sign(D) is possible, and, if it occurs at all, it will be only from minus to plus.

We have considered examples with logarithmically convex up or convex down functions for any value of their argument. But, taking into account real range of variation of the selected trait, some other situations can also be considered. For example, non-uniformity of the log-convexity within the range of the argument change is characteristic of the function $F(x) = (1 + (x-a)^2/s^2)^{-1}$ (Korol *et al.*, 1994). Here two domains of x exist with $F(x)$ log-convex up and down, correspondingly.

APPENDIX 1. PROOF OF LEMMA 1

Let us prove first the relationship (2) for some pair $i, i-1$. For this pair, the relationship (2) can be presented in the form

$$D^{(i)} = \Omega_{i,i-1}\,\Delta^{i-1|i-1}(1-r)\,x_1^{(i-1)}x_4^{(i-1)} + r\,\Delta^{i-1|i-1}\Omega_{i,i-1}\,C_{i-1}$$
$$+ (1-r)\,\Lambda_2^{i-1|i-1}\Lambda_3^{i-1|i-1}\Omega_{i-1\,i-1}\,D^{(i-1)}. \qquad \text{(A1.1)}$$

Substitution of

$$\Delta^{i-1|i-1} = \delta_{i-1}, \qquad \Omega_{i,i-1} = (W_{i-1}^{-2}),$$

and

$$C_{i-1}=[(1-\tau^{(i-1)})\,x_1^{(i-1)}x_4^{(i-1)}+x_2^{(i-1)}x_3^{(i-1)}\tau^{(i-1)}],$$

into (A1.1) gives a connection, which is essentially the same as that of Feldman (1971):

$$\begin{aligned}D^{(i)}=W_{i-1}^{-2}\{&\delta_{i-1}(1-r)\,x_1^{(i-1)}x_4^{(i-1)}+r\delta_{i-1}(x_1^{(i-1)}x_4^{(i-1)}(1-\tau^{(i-1)})\\&+x_2^{(i-1)}x_3^{(i-1)}\tau^{(i-1)})+(1-r)\,\lambda_{i-1,2}\lambda_{i-1,3}\,D^{(i-1)}\}.\end{aligned}$$

Now we shall prove that, if (2) holds for some pair j, i then it is true also for the pair j, $i-1$.

Employing the evolutionary operator (1), let us express $x_1^{(i)}x_4^{(i)}$ at the environmental state i in terms of the frequencies of the state $i-1$,

$$x_1^{(i)}x_4^{(i)}=\lambda_{i-1,1}\lambda_{i-1,4}\{x_1^{(i-1)}x_4^{(i-1)}(1-r)+rC_{i-1}\}\,W_{i-1}^{-2},$$

where

$$\begin{aligned}&C_{i-1}=(1-\tau^{(i-1)})\,x_1^{(i-1)}\,x_4^{(i-1)}+x_2^{(i-1)}x_3^{(i-1)}\tau^{(i-1)},\\&\tau^{(i-1)}=x_1^{(i-1)}+x_4^{(i-1)}-rD^{(i-1)}.\end{aligned}$$

Substitution of the last expression and of $D^{(i)}$ from (A1.1) into (2) results in:

$$\begin{aligned}D^{(j)}=\Omega_{ji}\,\Delta^{j-1|i}(1-r)^{j-i}\,\lambda_{i-1,1}\lambda_{i-1,4}\{&x_1^{(i-1)}x_4^{(i-1)}(1-r)\\&+rC_{i-1}\}\,W_{i-1}^{-2}+r\sum_{t=i}^{t=j-1}\Delta^{j-1|t}\Omega_{jt}(1-r)^{j-1-t}C_t\\&+(1-r)^{j-i}\Lambda_2^{j-1|i}\Lambda_3^{j-1|i}\Omega_{ji}\{\delta_{i-1}(1-r)\,x_1^{(i-1)}x_4^{(i-1)}\\&+r\,\delta_{i-1}C_{i-1}+(1-r)\,\lambda_{i-1,2}\lambda_{i-1,3}\,D^{(i-1)}\}\,W_{i-1}^{-2}.\end{aligned}\qquad\text{(A1.2)}$$

It is easy to check that the muliplier at $x_1^{(i-1)}x_4^{(i-1)}$ in (A1.2) is

$$\Omega_{j,i-1}\,\Delta^{j-1|i-1}(1-r)^{j-(i-1)},$$

because

$$\begin{aligned}\Delta^{j-1|i}\lambda_{i-1,1}\lambda_{i-1,4}+\Lambda_2^{j-1|i}\Lambda_3^{j-1|i}\,\delta_{i-1}&=\Delta^{j-1|i-1},\\\Omega_{j,i}\,W_{i-1}^{-2}&=\Omega_{j,i-1}.\end{aligned}$$

Also, the multiplier at $D^{(i-1)}$ in (A1.2) is

$$(1-r)^{j-(i-1)}\,\Lambda_2^{j-1|i-1}\Lambda_3^{j-1|i-1}\Omega_{j,i-1}$$

due to the simple fact that

$$\Lambda_2^{j-1|i}\Lambda_3^{j-1|i}\lambda_{i-1,2}^{(i-1)}\lambda_{i-1,3}^{(i-1)}=\Lambda_2^{j-1|i-1}\Lambda_3^{j-1|i-1}.$$

At last, the multiplier at C_{i-1} is

$$r\Omega_{j,it-1}\,\Delta^{j-1|i-1}(1-r)^{j-1-(i-1)}.$$

Therefore, we can obtain (2) from (A1.2) with i being replaced by $i-1$. This induction, together with the result for any pair $i, i-1$ proves the relationship (2).

The inequalities $\Omega_j, C_{jt} \geqslant 0$ are evident for all j and t. The inequality $0 \leqslant \tau^{(t)} \leqslant 1$ can also be easily proved.

We have only to show that (2′) is true. As in the previous case, we consider (2′) for the simplest pair $i, i-1$:

$$D^{(i)}=W_{i-1}^{-2}(\delta_{i-1}x_1x_4+(-r\delta_{i-1}\tau^{(i-1)}+\lambda_2\lambda_3(1-r))\,D^{(i-1)}). \qquad \text{(A1.3)}$$

Let now (2′) be true for some arbitrary pair j, i. As before, we can express $x_1^{(i)}x_4^{(i)}$ in terms of the frequencies in state $i-1$:

$$\begin{aligned} x_1^{(i)}x_4^{(i)} &= W_{i-1}^{-2}\lambda_1^{i-1}\lambda_4^{(i-1)}(x_1^{i-1)}-rD^{(i-1)})(x_4^{(i-1)}-rD^{(i-1)}) \\ &= W_{i-1}^{-2}\lambda_1^{i-1}\lambda_4^{(i-1)}(x_1^{(i-1)}x_4^{(i-1)}-r\,D^{(i-1)}\tau^{(i-1)}). \end{aligned}$$

Using the last expression and (A1.1) for substitution of $D^{(i)}$ by $D^{(i-1)}$ in the formula (2′), we will easily obtain the required relationship for the pair $j, i-1$.

The upper estimates for the quantities Ψ_{1ij} and Ψ_{2ij} immediately follow from the above-described procedure of induction, but they are rather cumbersome and therefore not given here. However, it is clear that Ψ_{1ij} and Ψ_{2ij} are finite sums of bounded quantities with the number of summands depending on the period length p. Thus, for any fixed p, one can indicate a small enough r such that (2′) takes place.

APPENDIX 2. PROOF OF LEMMA 2

For the sake of convenience we will formulate the lemma in the equivalent "multiplicative" form. Let

$$\alpha_i=\lambda_{i1}\lambda_{i4}/\lambda_{i2}\lambda_{i3} \qquad (i=1,\ldots,p) \qquad \text{(A2.1)}$$

be ordered circularly, and their product $\alpha_1\alpha_2\cdots\alpha_p$ exceed unity (i.e., $\Delta > 0$). In these terms, Lemma 2 means that a number i can be found such that all consecutive products

$$\alpha_i, \alpha_i\alpha_{i-1}, \alpha_i\alpha_{i-1}\alpha_{i-2}, ..., \alpha_i\alpha_{i-1}\cdots\alpha_{i-p+1}, \qquad \text{(A2.2)}$$

are no less than unity. This can be proved by induction. For $p = 1$ the statement is clear. Let it be true for a cycle of the length $p-1$. Consider the cycle of length p. From $\alpha_1\alpha_2\cdots\alpha_p > 1$ it follows that there exist some $\alpha_j > 1$. Then a sequence of $p-1$ elements can be obtained from the initial one (A2.1) with two elements α_{j-1} and α_j being substituted once by their product $\alpha_{j-1}\alpha_j$:

$$\alpha_1, \alpha_2, ..., \alpha_{j-2}, \alpha_j\alpha_{j-1}, \alpha_{j+1}, ..., \alpha_p.$$

Due to the condition of the induction, for this sequence a number i can be found such that all consecutive products (like in (A2.2)) are no less than unity. In this sequence the product $\alpha_i\cdots\alpha_{j+1}$ is followed immediately by $\alpha_i\cdots\alpha_{j+1}\alpha_j\alpha_{j-1}$. In the sequence of products (A2.2) corresponding to the intial sequence of the length p and beginning with the same position i, the elements $\alpha_i\cdots\alpha_{j+1}$ and $\alpha_i\cdots\alpha_{j+1}\alpha_j\alpha_{j-1}$ are separated by the element $\alpha_i\cdots\alpha_{j+1}\alpha_j$ and this is the only difference between the two sequences. We should mention in conclusion that $\alpha_i\cdots\alpha_{j+1}\alpha_j \geqslant 1$, because $\alpha_i\cdots\alpha_{j+1}$ belongs to (A2.2) with cycle length $p-1$ and, therefore, is $\geqslant 1$, while $\alpha_j \geqslant 1$ by assumption.

Thus, for $\Delta > 0$ the lemma is proved. The case $\Delta < 0$ can be considered in the same way.

Let now $\Delta = 0$, but at least one state exists with non-zero δ. By a small perturbation of fitness, we can obtain a value $\Delta = \tilde{\Delta}$ either negative or positive, depending on the chosen perturbation. If $\tilde{\Delta} > 0$ then according to the above result for $\Delta > 0$ a positive sequence of the type (A2.2) exists, while a negative one exists if $\tilde{\Delta} < 0$. It is important to note that these two sequences are different if at least one δ is non-zero. If $\Delta = 0$ and all δ are zeros, then in any sequence (A2.2) all the elements will be equal to 1, which is equivalent to the lemma (the case with some zero fitness coefficients can also be included in this reasoning based on limiting transition).

APPENDIX 3. PROOF OF PROPOSITION 1

For definiteness, assume $\Delta > 0$ and denote by s a positive environmental state. It should exist according to Lemma 2. For the state s, all fitness disequilibria $\Delta^{5|5-j}$ $(j=1, 2, \ldots p)$ are non-negative and from $\Delta>0$ it follows that at least one of these coefficients is strictly positive. Then, the quantity

$$\Omega_{ji}\,\Delta^{j-1|i}(1-r)^{j-i}\,x_1^{(i)}x_4^{(i)}+r\sum_{t=i}^{j-1}\Delta^{j-1|t}\Omega_{jt}(1-r)^{j-t-1}C_t$$

from (2) is also non-negative. So, according to (2), if $D^{(i)}$ is non-negative in a period it will have the same sign in all subsequent periods. It means also that sign(D) can be changed only once (in this case, from minus to plus). If, in the environmental state s the initial value of D was positive, then according to the above, the sign of D will remain unchanged along the trajectory. Now we should show that, if the intial D is negative, it will change the sign for a finite number of steps.

Consider two situations. Let in the initial cycle at least one value of D be positive (denote this state as j). In the formula (2) connecting the states j and s all coefficients are non-negative, because s is a positive state. Thus, in the next period D will also became non-negative. Let us now assume that in all states along the initial cycle $\operatorname{sign}(D)<0$. For any pair of consequent states the relation

$$\frac{x_1'x_4'}{x_2'x_3'}=\frac{\lambda_1\lambda_4(x_1-rD)(x_4-rD)}{\lambda_2\lambda_3(x_2+rD)(x_3+rD)}$$
$$=\xi\,\frac{x_1x_4-rD(x_1+x_4-rD)}{x_2x_3+rD(x_2+x_3+rD)},\qquad \left(\xi=\frac{\lambda_1\lambda_4}{\lambda_2\lambda_3}\right)$$

holds, and then

$$\frac{x_1'x_4'}{x_2'x_3'}\geqslant\xi\,\frac{x_1x_4}{x_2x_3},$$

because with $D>0$ the quantities $rD(x_1+x_4-rD)$ and $rD(x_2+x_3+rD)$ are non-positive. By iteration of this inequality along the cycle we will get

$$\frac{x_1^{(s+i)}x_4^{(s+i)}}{x_1^{(s+i)}x_4^{(s+i)}}\geqslant\Xi_i\,\frac{x_1^s x_4^s}{x_1^s x_4^s},\qquad (i=1, 2, \ldots, p)\qquad\text{(A3.1)}$$

where $\Xi_i=\Lambda_1^{(s+i)}\Lambda_4^{(s+i)}/\Lambda_2^{(s+i)}\Lambda_3^{(s+i)}\geqslant1$ due to the assumption that $\Delta^{s|s-j}\geqslant0$ (it is worth noting that Ξ_j is, in fact, the multiplicative form of $\Delta^{s|s-j}$). For at least one j the quantity $\Delta^{s|s-j}$ is strictly positive, so that $\Xi_j\geqslant1$. Thus, according to (A3.1), the value of D increases exponentially and after a finite number of steps D will become positive at least in one of the environmental states. This situation can be considered as an initial one for the above-considered case. The case with $\Delta<0$ can be considered analogously.

Let $\Delta = 0$. We should analyze here two situations. Consider first the case when $\delta \neq 0$ at least in one of the states. According to Lemma 2 in this case both positive and negative states exist. The above reasoning can be applied to each of them. If $\Delta = 0$ and for all states $\delta = 0$, then the proposition follows immediately from the formula (2) of Lemma 1.

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