J. theor. Biol. (1998) **190,** 215–225

Complex Limiting Behaviour of Multilocus Genetic Systems in Cyclical Environments

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(*Received on* 7 *January* 1997, *Accepted in revised form on* 16 *September* 1997)

Here we demonstrate that complex limiting behaviour (supercycles and chaotic-like phenomena) may arise in a rather broad and natural class of multilocus systems, both haploid and diploid, experiencing stabilizing selection with cyclically varying optima over a short period. These include loci with purely additive, dominant, or semidominant effects, with different types of their chromosome distribution. The observed complex dynamics appeared to manifest a certain stability with respect to disturbances of parameters specifying the structure of the selected system and environmental characteristics. This mode of multilocus dynamics by far exceeds the potential attainable under ordinary selection models resulting in simple behaviour. It may represent a novel evolutionary mechanism increasing genetic diversity over long time periods. This novel mechanism could contribute to the observation that biological diversity has increased over geological time regardless of the well-known massive extinctions.

1. Introduction

We found earlier that cyclical selection with a short period may induce autooscillations with a long period ("supercycles") (Kirzhner *et al*., 1994, 1995b). In all of the foregoing two-locus discrete-time systems, these supercycles appeared to be possible for narrow ranges of parameters. Later, we tried to overcome this limitation. As a result, a very natural class of models was discovered where cyclical selection generates complex limiting behaviour, including supercycles and chaotic-like phenomena (Kirzhner *et al*., 1996).

This class involves different forms of multilocus stabilizing selection with cyclically moving optimum. Stabilizing selection is one of the major models of population genetics and many efforts were devoted to its theoretical analysis in the last decade (Burger, 1989; Turelli & Barton, 1990; Zhivotovsky & Feldman, 1992; Gavrilets & Hastings, 1994a). Stabilizing selection in temporally changing environments has also attracted the attention of theoreticians, especially in view of the interest in recombination evolution (Maynard Smith, 1988; Charlesworth, 1993; Korol *et al*., 1994). In particular, these authors have shown that cyclical selection can maintain recombination. Earlier, Lande (1976), assuming loose linkage and weak selection reached the conclusion that stabilizing selection with temporally moving optimum does not help in the maintenance of genetic variation. This leads to a generalization that a temporally changing environment is, in itself, not sufficient as a factor of recombination evolution (e.g. Kondrashov, 1993). Our results indicate that either a change in the form of the fitness function, or using non-equal additive genes or genes with a dominance effect, relax the problem of polymorphism maintenance (Kirzhner *et al*., 1995a; Korol *et al*., 1994, 1996). As a rule, this is possible under sufficiently strong selection and/or relatively close linkage. Consequently, stable polymorphism is accompanied by linkage disequilibria. This may help in a re-evaluation of different

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hypotheses of recombination evolution (Korol *et al.*, 1994). Recently, Kondrashov & Yampolsky (1996) also considered cyclical selection for many loci of equal effect assisted by mutation flow as a mechanism of polymorphism maintenance. It is not known, however, whether polymorphism will be protected in an analogous mutation-free system. Our recent simulations showed that the proposed earlier mechanisms of polymorphism maintenance in infinite populations due to non-equal gene effects or semi-dominance may help in long-term polymorphism maintenance at many loci in finite populations as well (Nevo *et al.*, 1997).

The results obtained in these studies demonstrate a remarkable property of cyclical selection concerning the conditions of polymorphism maintenance: the realistic patterns in nature, i.e. non-equal effects and deviation from purely additive within-locus scheme of gene action, appear to promote polymorphism. Either of these two conditions is an important component of polymorphism protection in the considered model, otherwise cyclical selection is unable to maintain polymorphism at any selection stringency and tightness of linkage with an exception of some special cases (for two locus analysis see: Kirzhner *et al.*, 1995a; Korol *et al.*, 1996).

Consequently, it may be of general interest to consider in more detail the unusual form of polymorphism existence referred to as "complex limiting behaviour" (CLB) that was revealed in our previous paper (Kirzhner *et al.*, 1996). Here we will: (a) present a wide spectrum of selection models and genomic configurations of the selected loci (their chromosome distribution) compatible with CLB; and (b) analyse the robustness of CLB with respect to disturbances in the period length, selected trait values, and haplotype frequencies.

2. The Model

We examine the behaviour of an infinite population with panmixia, non-overlapping generations, and several linked diallelic loci, A_i/a_i $(i = 1, \ldots, L)$ affecting the selected trait, u. Consider a genotype g with $u = u(g)$ defined as: $u(g) = \sigma\sum_i u_i(g)$, where the effect of the ith locus of the genotype g is specified as:

$$u_i(g) = \begin{array}{ll} d_i, & \text{for } A_iA_i \quad (d_i > 0) \\ 0.5\, d_i(1 + h_i), & \text{for } A_ia_i, \\ 0, & \text{for } a_ia_i. \end{array}$$

Clearly, this scheme describes additive control of the selected trait u across loci with an arbitrary level of dominance within loci. For cyclical selection, the fitness $w_t(u)$ of a genotype with trait value u at the environmental state t is defined by the fitness function

$$w_t(u(g)) = F(u(g) - z_t),$$

where z_t is the trait optimum selected for at the moment t. For example one can use $F(u(g) - z_t) = \exp\{-[u(g) - z_t]^2/s^2\}$, a fitness function which is widespread in population genetics.

The evolutionary equations for the environmental state t can be written in the standard form:

$$x'_m = \sum_{ij} w_t(u(g_{ij}))P_{ij,m}x_ix_j/W, \tag{1}$$

where x and x' are gamete frequencies in adjacent generations; W is the mean fitness; $P_{ij,m} \geqslant 0$ is the probability of producing gamete m by a heterozygote g_{ij} that resulted from union of gametes i and j, $\sum_m P_{ij,m} = 1$. The frequency $P_{ij,m}$ of haplotype m can easily be calculated as a sum of the frequencies of elementary events resulting in its appearance from the zygote g_{ij}.

The above system was studied numerically, under different types of cyclical selection regimes, conditioned by an ordered set $\{z1|n1, z2|n2, \ldots, zq|nq\}$, where z_t is the selected optimum at the tth environmental state, n_t is the longitude of the tth state, and $p = n_1 + n_2 + \cdots + n_q$ is the period length.

3. Results: Selection Models (Modes) Resulting in CLB

Earlier we showed that a broad spectrum of CLB modes could be obtained with cyclical diploid selection for a trait controlled by a block of few (e.g. four) linked loci (Kirzhner *et al.*, 1996). Besides, CLB regimes were found in haploid two locus systems with cyclical selection and special fitness matrices (Kirzhner *et al.*, 1994). The objective of this paper is to show that stabilizing selection with cyclically varying optimum generates CLB in either diploid or haploid systems with different configurations of the selected loci (according to their chromosome distribution). We will demonstrate, that these movements are quite resistant to different types of disturbances. Our other goal here is to provide a kind of an "anthology" of CLB modes generated within a class of simple natural models of cyclical selection for a multilocus selected trait (we confine the analysis to four loci).

3.1. DIPLOID SELECTION FOR ADDITIVE GENES WITH NON-EQUAL EFFECTS

For the case of purely additive loci only unequal effects of the participating loci were considered, because with additive loci of equal effects polymorphism cannot be maintained for "usual" fitness functions (like Gaussian or quadratic parabola) (Gavrilets & Hastings, 1994b; Korol *et al.*, 1994, 1996). In Fig. 1 we demonstrate a spectrum of CLBs for three types of positioning of selected loci: a block of four linked loci [Fig. 1(a–d)], two unlinked blocks, each consisting of two linked loci (Fig. 1(e, f)], and four unlinked loci [Fig. 1(h)]. Beside four-locus systems [Fig. 1(a–h)], examples with three and six loci are presented as well [Fig. 1(i, j)].

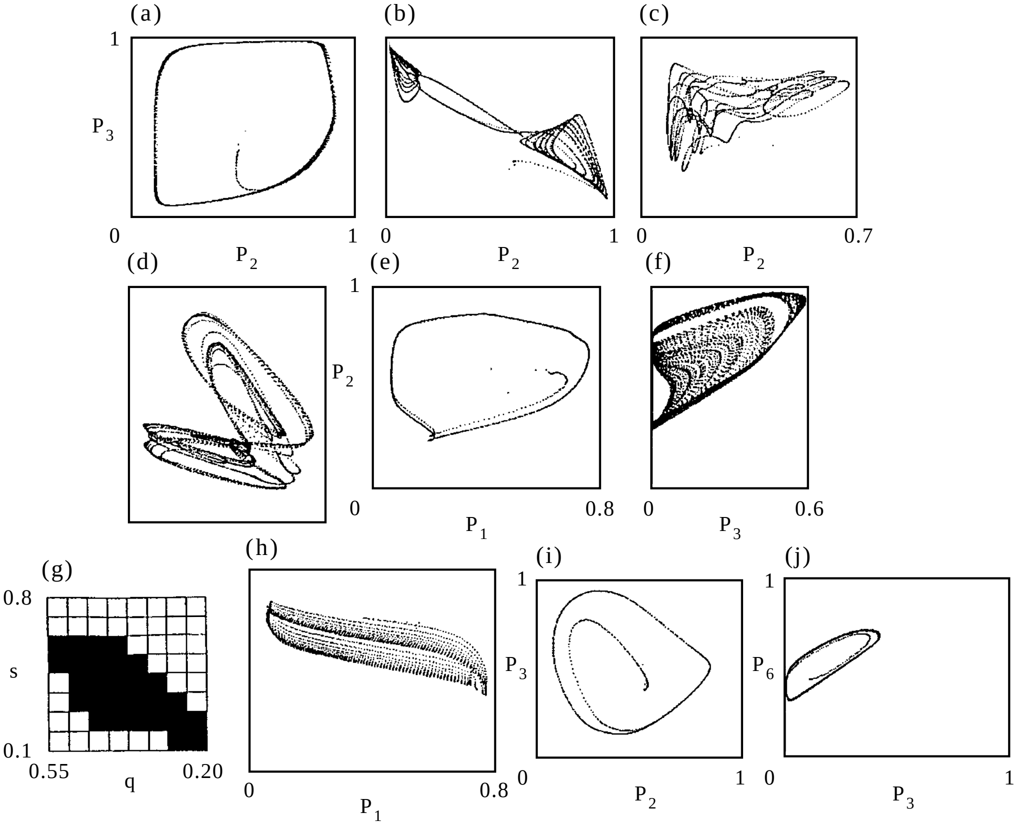

FIG. 1. Complex population trajectories caused by cyclical diploid selection for a trait controlled by four additive loci with unequal effects. Here and in all other figures, the points representing the system phase state (allele frequencies at two out of the four loci) are sampled only at time multipliers of the environmental period length p. Thus, a full cycle of the environment is marked by the end-point of the period. The haplotype frequencies at the initial points of the trajectories will be presented below (if necessary) in the following order (1111, 1011, 0111, 0011, 1101, 1001, 0101, 0001, 1110, 1010, 0110, 0010, 1100, 1000, 0100, 0000), where 1 or 0 at position i ($i = 1, \dots, 4$) stands for A_i or a_i, respectively. The intial points here and in the subsequent figures correspond to $z = z_1$ and are given with an accuracy to a normalizing constant (i.e. the presented coordinates should be divided by their sum). Figures (a–h) correspond to four-locus systems: (a–d)—a single linkage group; (e) and (f)—two unlinked blocks each with two linked loci, (h)—four unlinked loci; (i) and (j) correspond to systems with three and six linked loci, respectively. In all cases the simple period structure $n_1 = 1$, $n_2 = 0$, $n_3 = 1$ was employed. (a) A simple supercycle: $s = 2.0$, $r = 0.3$, $d_1 = 3.4$, $d_2 = 1.6$, $d_3 = 0.4$, $d_4 = 0.1$; $z_1 = 11$, $z_3 = 0$. Note the wide range of changes of allele frequencies along the supercycle; the scaled linkage disequilibria D'_{ij} between the neibouring loci at the environmental state 2 varied along the supercycle in the range 0.06–0.43, 0.08–0.002, and 0.002–0.001 for D'_{12}, D'_{23}, and D'_{34}, correspondingly. (b) A complex two-component supercycle: $s = 0.42$, $r = 0.045$, $d_1 = 1.0$, $d_2 = d_3 = d_4 = 0.3$; $z_1 = 3.8$, $z_3 = 0$. This cycle consists of two parts. With some changes in the model parameters we can split this CLB into two separate cycles or to obtain one central cycle. The scaled linkage disequilibria D'_{ij} between the neibouring loci at the environmental state 2 varied along the supercycle in the range 0.01–0.40, 0.03–0.35, and 0.02–0.21 for D'_{12}, D'_{23}, and D'_{34}, correspondingly. (c) Non-cyclical complex trajectory. The parameter values used here were: $d_1 = 2.3$, $d_2 = 1.8$, $d_3 = 1.6$, $d_4 = 1.2$, $s = 1.85$, $r = 0.012$, $z_1 = 16.8$, $z_2 = -3$. The initial point in the presented trajectory was (.001855 .000000 .061224 .005566 .064935 .038961 .098330 .035251 .129870 .174397 .050093 .081633 .018553 .128015 .103896 .007421). (d) The same system as in Fig. 1(c) is presented here, but projected to another plane. (e) A supercycle in a system with two linked blocks: (1,2) and (3,4); $s = 2.3$, $r = 0.1$, $d_1 = 0.5$, $d_2 = 1.6$, $d_3 = 4.4$, $d_4 = 1.1$; $z_1 = 15.2$, $z_3 = 0$. The scaled linkage disequilibria D'_{ij} between the neibouring loci at the environmental state 2 varied along the supercycle in the range 0.001–0.10, 0.01–0.25, and 0.01–0.50 for D'_{12}, D'_{23}, and D'_{34}, correspondingly. (f) A complex attractor for a system with two linked blocks: (1,2) and (3,4); $s = 2.0$, $d_1 = 1.5$, $d_2 = 1.4$, $d_3 = 4.3$, $d_4 = 1.2$. In the first block $r = r_1 = 0.0136$, in the second $r = r_2 = 0.1$, $z_1 = 16.9$, $z_3 = -0.5$. We show the part of the trajectory for 20,000 environmental periods (from 30,001 to 50,000). (g) The set of parameters resulting in CLB. Here q characterizes the ratios of the individual loci effects; $r = 0.1$ was taken in the simulations, but a close pattern was obtained up to $r = 0.3$. (h) A fragment of a trajectory converging to a simple supercycle in a system with four unlinked loci: $s = 1.65$, $d_1 = 0.1$, $d_2 = 0.4$, $d_3 = 1.6$, $d_4 = 4.4$, $z_1 = 13$, $z_3 = 0$. (i) A simple supercycle in a model with three linked loci: $s = 0.25$, $r = 0.33$; $d_1 = 0.1$, $d_2 = 0.4$, $d_3 = 0.2$, $d_4 = 0.0$, $z_1 = 1.45$, $z_3 = 0.15$. (j) A simple supercycle in a model with six linked loci: $s = 0.41$, $r = 0.1$; $d_1 = 0.01$, $d_2 = 0.02$, $d_3 = 0.06$, $d_4 = 0.14$, $d_5 = 0.33$, $d_6 = 0.80$, $z_1 = 2.72$, $z_3 = 0$.

Figure 1(a) demonstrates a simple supercycle with a wide range of changes in the phase parameters along the trajectory. It would be of great interest to understand the nature of this CLB. We found that this cycle can be obtained by varying the bifurcation parameter r (recombination rate). With $r = 0.14$ we have a stable polymorphic point. Numerical analysis of the Jacobian of the transformation (1), iterated over the environmental period, has shown the existence of an eigenvalue $0.9973 \pm 0.0221i$, the remainder elements of the spectrum being real. Theoretically, it means that a cyclical movement with a period of about 280 environmental periods can be obtained. In fact, a result close to this prediction was observed at $r = 0.3$: a supercycle with period length of 270, that is presented in Fig. 1(a). The more complex supercycle of Fig. 1(b) consists of two-dimensional components that lie in different planes, with two alternative sets of three-to-four haplotypes predominating in the population. With an exception of a small domain close to the border set, any arbitrary initial point results in a trajectory that converges to this supercycle. Moreover, this system manifests also a rather high parametric stability. Thus, within a certain range of variation in selection intensities and recombination rates, the majority of trajectories converge to CLB (e.g. this occurred in 50 cases from 50 random starts, for each of the following three sets: $s = 0.3$ and $0.1 < r < 0.5$; $s = 0.4$ and $0.1 < r < 0.4$; and $s = 0.5$ and $0.2 < r < 0.3$).

A complex non-cyclical trajectory is presented in Fig. 1(c). This limiting chaotic-like motion belongs to an eight-dimensional plane. A small perturbation of the coordinates of the initial point leads to an increasing divergence over time of the resulting trajectory as compared to the initial (non-disturbed) trajectory. Some other two-dimensional projections could be found where the trajectories look like a chaotic attractor. Figure 1(d) displays two domains of attraction; consequent switching of the trajectory between these domains appears to be non-regular and reminds of the classical Lorenz attractor. Two unlinked blocks of genes can also produce chaotic-like behaviour as illustrated in Fig. 1(f). For the last example we also have attempted to represent the appearance of the CLB as a result of bifurcation a polymorphic fixed point caused by change in bifurcation parameter s (the presented CLB was obtained at $s = 2.0$ whereas $s = 1.75$ results in a stable polymorphic point). Noteworthy, that the spectrum of linear approximation at this point contains three complex eigenvalues. The last peculiarity may be an indicator of the system's ability to manifest complex behaviour after loosing the stability of the fixed point.

It would be of great interest to know more on how generic the CLB phenomenon for diploid models is with non-equal additive genes subjected to cyclical selection. In light of this question, we have evaluated the proportion of CLB-manifesting systems in a special subset of systems with non-equal effects. Namely, consider a system of four linked additive genes, and let the effects of genes be in a progression $1{:}q{:}q^2{:}q^3$. For each chosen rate of recombination (r) we evaluated the set of (s, q)-pairs resulting in CLB in at least one of 10 random starts, when the system was subjected to a cyclical selection regime with period 1:1 (e.g. $n_1 = n_3 = 1$, and $n_2 = 0$) and the selected trait values were $m_1 = 2(1 + q + q^2 + q^3)$ and $m_3 = 0$. It appears, that at least for the considered sub-class of systems with additive gene action, CLB is not a rare phenomenon [Fig. 1(g)].

The next group of questions concerns the stability of CLB to random fluctuations of parameters characterizing the environment. We examined two aspects: changes in selected optimum trait values and changes in the period length (Fig. 2). Cyclical selection with a basically two-state environment was considered. The first question is the effect of random fluctuations of the optimum values of the trait. As before, the period structure is 1:1, but the deterministic selected value z_1 is replaced by an evenly distributed random variable with mean value z_1. In our example [Fig. 2(a–c)], the maximum of the spectral densities of the resulting ("disturbed") trajectories is close to that of the undisturbed system. Similar results were obtained when the period itself is randomly disturbed [Fig. 2(d–f)]. In this case the values z_1 and z_3 are deterministic, but the ratio 1:1 of the period structure is stochastically changing to 2:1 or 1:2 or 2:2 with some probabilities. As can be seen from the presented examples, CLB is quite resistant to such interruptions, if their frequency is not too large.

3.2. HAPLOID SELECTION FOR ADDITIVE GENES WITH NON-EQUAL EFFECTS

Clearly, considering fluctuating selection (temporal or spatial) is of special interest for haploid selection models, as the simplest mechanism of polymorphism maintenance in such systems (Kirzhner *et al*., 1995a). As applied to our subject (complex limiting behaviour), haploid population models provide a unique opportunity to exclude any hidden causal effect of heterozygosity. Actually, the first examples of this type were found earlier, but not in the framework of cyclical selection for an additively controlled trait (Kirzhner *et al*., 1994).

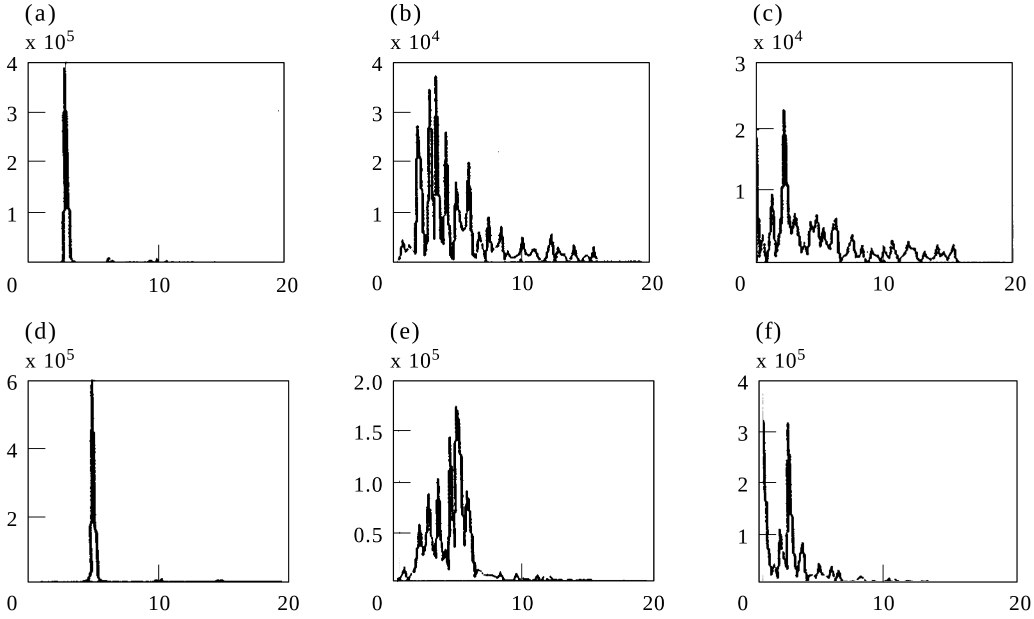

FIG. 2. Changes in spectral densities of supercyclical movements in two systems with additive loci caused by random disturbances of environmental parameters. I. Random variations of z_1 for a selected system with four linked additive loci with $s = 0.425$, $r = 0.007$; $d_1 = 1$, $d_2 = d_3 = d_4 = 0.3$; $n_1 = 1$, $n_2 = 0$, $n_3 = 1$, $z_1 = 3.8$, $z_3 = 0$; (a) undisturbed process, (b) 10% range of variation, (c) 50% range of variation. II. Random variations of period length for a selected system with four unlinked additive loci with effects $d_1 = 0.1$, $d_2 = 0.4$, $d_3 = 1.6$, $d_4 = 4.4$; $s = 1.65$; $n_1 = 1$, $n_2 = 0$, $n_3 = 1$; $z_1 = 13$, and $z_3 = 0$ [see Fig. 1(h)]; (d) undisturbed process, (e) with a probability of $\pi = 0.1$ along the trajectory, n_1 or n_2 become independently equal to 2; (f) the same as (b) but $\pi = 0.15$.

In Fig. 3(a) we demonstrate a supercycle in a system with four equally spaced closely linked loci. This is an example of CLB caused by alternating variations in the selected trait value. In our previous example of supercyclical oscillations in haploid two locus systems (Kirzhner *et al.*, 1994) the structure of the environmental period was rather complex, and only damping autooscillations were observed upon simple period structure. Allowing for non-equal lengths of adjacent chromosomal intervals results in a more complicated set of limiting trajectories. For example, we obtained two stable supercycles (one included in the other), as shown in Fig. 3(b). Figure 3(c) demonstrates a supercycle in a system with two unlinked two-locus blocks. In contrast to diploid selection, no examples of CLB were found for four

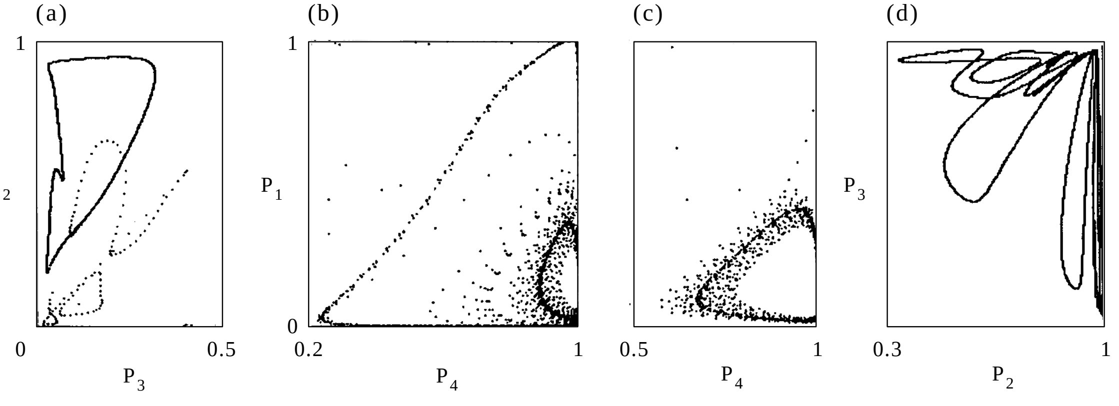

FIG. 3. Supercycles caused by cyclical haploid selection for a trait controlled by four additive loci with unequal effects. (a) A simple supercycle in a system with four linked loci; $s = 0.167$, $r = 0.007$; $d_1 = 0.18$, $d_2 = 0.1$, $d_3 = 0.17$, $d_4 = 0.23$; $n_1 = 3$, $n_2 = 0$, $n_3 = 3$; $z_1 = 0.846$, $z_3 = -0.15$. (b) Two stable supercycles in a system with two loosely linked blocks ($r_2 = 0.4$) each consisting of two tightly linked loci ($r_1 = r_3 = 0.0012$); $s = 0.125$; $d_1 = 0.12$, $d_2 = 0.16$, $d_3 = 0.18$, $d_4 = 0.23$; $n_1 = 3$, $n_2 = 0$, $n_3 = 3$; $z_1 = 1.04$, $z_3 = -0.20$. (c) A supercycle in a system with two unlinked blocks each consisting of two tightly linked loci; $s = 0.15$, $r = 0.0012$; $d_1 = 0.12$, $d_2 = 0.16$, $d_3 = 0.18$, $d_4 = 0.23$; $n_1 = 3$, $n_2 = 0$, $n_3 = 3$; $z_1 = 1.04$, $z_3 = -0.18$. (d) A complex supercycle in a system with four linked loci: $s = 0.0725$, $r = 0.002$; $d_1 = 0.18$, $d_2 = 0.1$, $d_3 = 0.17$, $d_4 = 0.23$; $n_1 = 1$, $n_2 = 0$, $n_3 = 1$; $z_1 = 0.35$, $z_3 = -0.005$.

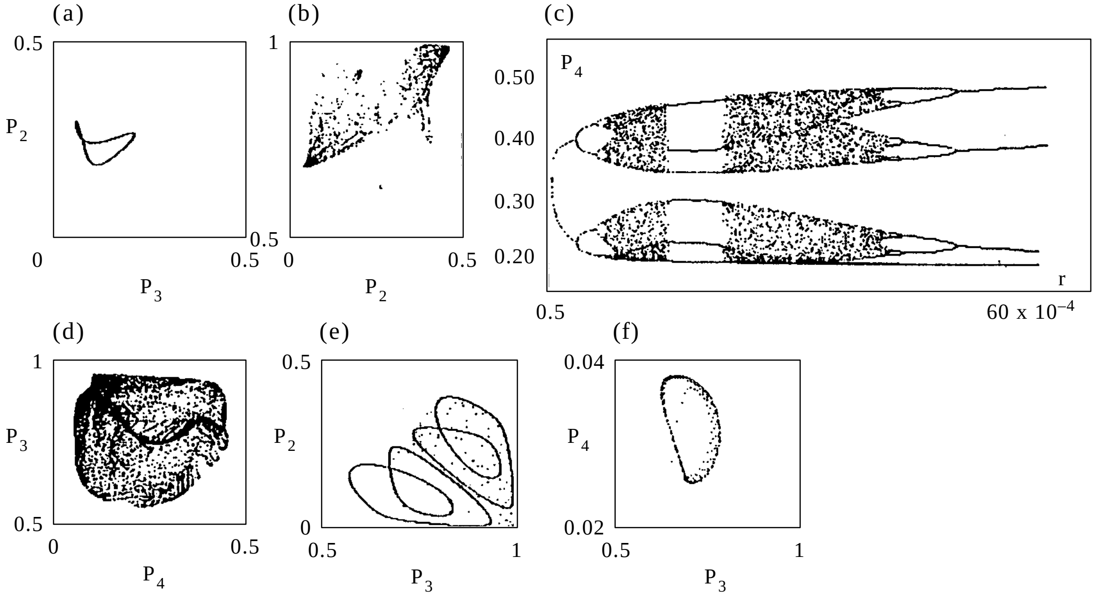

FIG. 4. Complex trajectories caused by cyclical selection for a trait controlled by four (semi)dominant loci. (a) A simple supercycle: $s = 0.86$, $r = 0.026$; $d_1 = d_2 = d_3 = d_4 = 1$, $h_1 = 0.15$, $h_2 = 0.35$, $h_3 = 0.40$, $h_4 = 0.40$; $n_1 = 2$, $n_2 = 0$, $n_3 = 1$; $z_1 = 3.0$, $z_3 = 0$. (b) Chaotic-like behaviour: $s = 0.5$, $r = 0.03$, $z_1 = 4.0$, $z_2 = 2.2$, $z_3 = 0.1$, $h_1 = h_2 = h_3 = h_4 = 0.5$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$. The conclusion about chaotic-like regime is derived from the known criterion of trajectory divergence caused by perturbation of the initial point. The initial point in the presented trajectory was (.000 .000 .000 .001 .000 .001 .013 .331 .000 .000 .002 .180 .001 .075 .388 .008). The range of r resulting in CLB was [0.01–0.05]. Within this range, T-supercycles were also observed. (c) Bifurcation diagram for the example (b) with r taken as bifurcation parameter. The initial point was (.000000 .000000 .00000 .000010 .000013 .000000 .358222 .000000 .000010 .000000 .275081 .000000 .0.000016). (d) A complex attractor for a sytem with four linked loci; $s = 0.89$, $r = 0.079$; $d_1 = d_2 = d_3 = d_4 = 1$; $h_1 = 0.16$, $h_2 = 0.34$, $h_3 = 0.34$, $h_4 = 0.38$; $n_1 = 2$, $n_2 = 0$, $n_3 = 1$; $z_1 = 3.0$, $z_3 = 0$. We show the part of the trajectory for 20,000 environmental periods (from 20,001 to 40,000). (e) Two "twin" supercycles in a system with dominance varying across environments: $s = 0.4$, $r = 0.015$, $h_i = -0.7$ or 0.7, for the environmental states with $z_1 = 4.04$, $z_3 = -1.0$, respectively; $n_1 = 1$, $n_2 = 0$, $n_3 = 3$. Starting from two different points (A and B) we found two symmetrical trajectories: $A =$ (.908 .008 .002 .006 .008 .006 .001 .005 .008 .008 .007 .006 .005 .009 .009); $B =$ (.007 .002 .003 .008 .002 .005 .005 .935 .005 .002 .002 .004 .008 .003 .007). (f) A simple supercycle in a system with two unlinked blocks of linked genes: $n_1 = n_3 = 1$, $n_2 = 0$. $z_1 = 3.7$, $z_3 = -0.2$. $s = 0.75$, $r = 0.001$. $h_1 = 0.48$, $h_2 = -0.27$, $h_3 = 0.22$, $h_4 = -0.5$; the initial points were (.002 .000 .061 .005 .065 .039 .098 .035 .130 .170 .050 .082 .019 .128 .104 .007).

unlinked loci under haploid selection regimes. An important fact is that cyclical haploid selection may also produce more complex behavioural patterns. One such example is presented in Fig. 3(d). In spite of its quite complex pattern, the presented attractor is close to a cycle, however trajectories with close starting points tend to diverge with time.

3.3. DIPLOID SELECTION FOR SEMI-DOMINANT GENES

We consider here the same model, but assume that the selected trait is controlled by semi-dominant loci ($h_i \neq 0$) with equal effects. The main difference of the regimes produced by this assumption is that T-supercycles (i.e. short supercycles with *exact* repeat of the phase states after T environmental periods) and chaotic-like behaviour are the common modes of the manifested CLB (Fig. 4). As before, more than one mode of CLB can be manifested by one system, depending on the initial point.

Figure 4(a) represents a simple supercycle, whereas an example of a complex chaotic-like attractor is given in Fig. 4(b). The bifurcation diagram of the latter (with recombination rate taken as the bifurcation parameter) consists of a series of transformations of chaotic-like behaviour into T-supercycles and backward. A complex non-cyclical (non-converging) trajectory is shown in Fig. 4(d). It is noteworthy, that the volume of attraction of these CLBs (the proportion of initial points resulting in such trajectories) is quite high, approaching 50–90%. From the biological point of view, it is interesting that the range of changes in the phase parameters (allele frequencies) along the trajectories is also quite wide. Figure 4(e) shows two trajectories corresponding to two nice symmetrical supercycles. This behaviour was found in a system with dominance varying across environments, a temporal analogue of Gillespie's (1978) model with spatially varying environment. The last example in Fig. 4(f) represents a situation with stable (unchanging) dominance in a system with two unlinked blocks each consisting of two tightly linked loci. Our trials to make the next step, with four unlinked loci, failed to reveal any CLB.

Consider now the question of *stability of CLB to random fluctuations*. As for the model with unequal additive genes, we analysed the effect of random fluctuations of the modal values of the selected trait. The deterministic selected value z_1 was replaced by evenly distributed random variable with mean value z_1. One can easily see (Fig. 5) that with moderate deviations from the mean z_1 (up to 25% of the initial deterministic value of z_1), the resulting movement preserves to a large extent the behavioural mode characteristic to the non-disturbed deterministic system [compare Fig. 5(a) and (b) for both model systems, I and II]. The same conclusion was reached with respect to disturbances caused by random fluctuations of the period length [compare Fig. 5(a) and (c) for both models]. Therefore, we can conclude, that CLB manifest certain robustness with respect to moderate random disturbances of selection regime.

Of special separate interest is the question of stability of CLB to random drift caused by *finite population size*. In contrast to the foregoing examples of stability against random disturbances of model parameters, introduction of fluctuations caused by finite population size means actually a change in the basic model. We consider this question using as an example a model with three semidominant loci. In order to analyse the robustness of CLB to finite population size, the following procedure was employed: at each generation, the vector of haplotype frequencies was disturbed by a vector of "sampling errors" with the coordinates simulated as random normal variables with zero expectations and variances equal to $\delta^2(x_i) = x_i(1 - x_i)/N$, where N is the "simulated" population size. Another approach to simulate a finite population size was an introduction of minimal haplotype frequency border x^o, so that at any generation any haplotype frequency that appeared to be less than x^o, is replaced by zero. Figure 6 illustrates the results. As one can see, for the considered example, population sizes from $N = 5000$ and higher display the same pattern of CLB as the non-disturbed (infinite) population. An interesting phenomenon is that the finite population manifests simultaneously both CLBs to which the infinite population converges alternatively, i.e. when starting from different initial points. Clearly, the last phenomenon is possible due to random fluctuations of the trajectory that allow it to appear alternatively in the domain of attraction of each of the CLBs. With increasing N, this effect disappears, and the trajectory

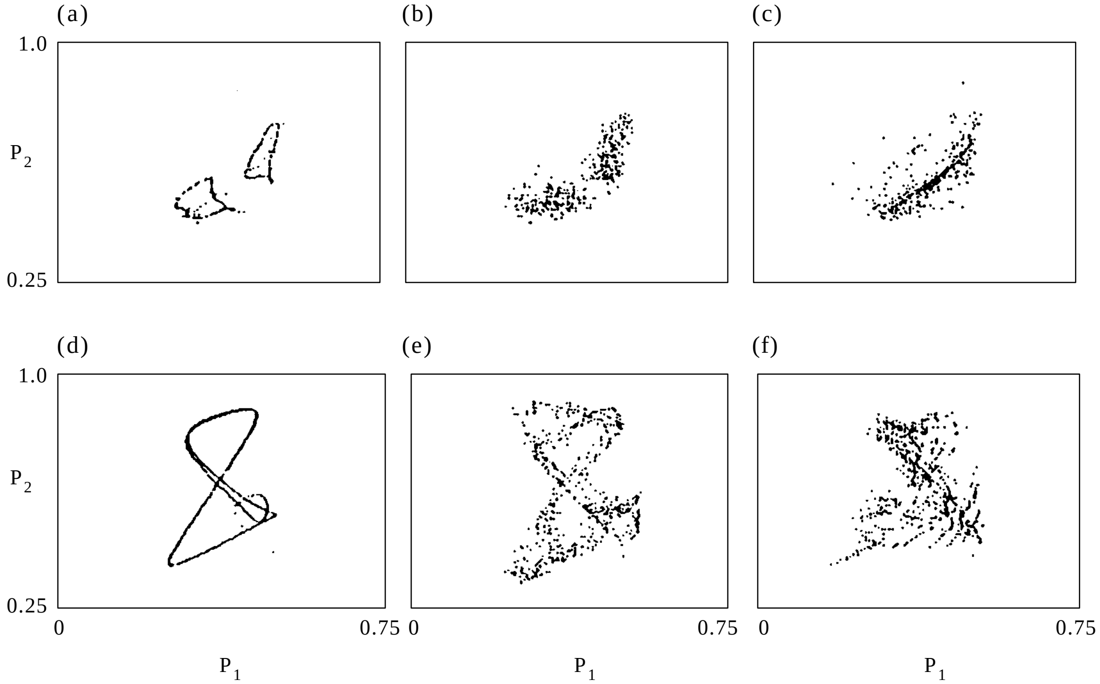

FIG. 5. Changes in phase diagrams of supercyclical movements in two systems with dominant loci caused by random disturbances of environmental parameters. (a) Undisturbed process—T-supercycle in selected system with four linked additive loci with $s = 0.7$, $r = 0.05$; $d_1 = d_2 = d_3 = d_4 = 1.0$; $h_1 = h_2 = h_3 = h_4 = 0.5$, $n_1 = n_2 = n_3 = 2$, $z_1 = 4.0$, $z_2 = 2.4$, $z_3 = 0$; (b) Random variations of z_1 (range 25%); (c) Random variations of period length: with a probability of D = 0.5 along the trajectory, n_1, n_2 or n_3 become independently equal to 1. (d) Undisturbed process—a simple supercycle in selected system with four linked semidominant loci with effects $s = 1.2$, $r = 0.006$; $d_1 = d_2 = d_3 = d_4 = 1.0$; $h_1 = h_2 = h_3 = 0.18$, $h_4 = -0.5$; $n_1 = n_3 = 1$, $n_2 = 0$, $z_1 = 3.04$, $z_3 = 0.2$. (e) Random variations of z_1 (range 25%). (f) Random variations of period length: with a probability of D = 0.1 along the trajectory, n_1, or n_3 become independently equal to 2.

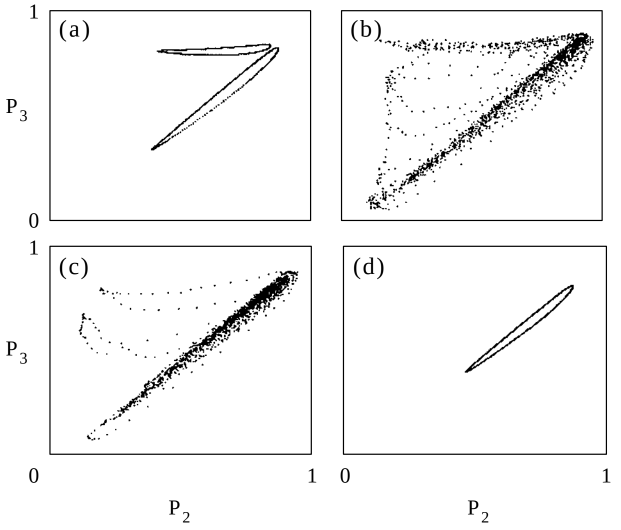

FIG. 6. Changes in phase diagrams of supercyclical movements in a system with three semi-dominant loci caused by genetic drift. (a) Two limiting supercyclical trajectories in the undisturbed (infinite) population corresponding to different sets of initial points: $s = 0.84$, $r = 0.02$; $d_1 = d_2 = d_3 = d_4 = 1.0$; $h_1 = h_2 = 0.15$, $h_3 = -0.195$; $n_1 = n_3 = 1$, $n_2 = 0$, $z_1 = 3.3$, $z_3 = 0.3$. It is noteworthy, that the size of the attraction domain of cycle 1 is several times larger than that of cycle 2. (b) The trajectory of the system with random disturbances of the haplotype frequencies simulating the effect of drift with population size $N = 5000$; (c) the trajectory of the system with random disturbances of the haplotype frequencies simulating the effect of drift with population size $N = 10000$; (d) the limiting set of system's trajectories with a minimal border of haplotype frequencies: at each generation all haplotype frequencies with a value less than $x^o = 0.001$ were replaced by zero.

becomes associated with only one of the possible CLBs.

Discussion

Temporal environmental fluctuations has for a long time attracted much attention as a factor of polymorphism maintenance. Theoretical analysis of single-locus models has delimited the conditions of polymorphism (Haldane & Jayakar, 1963; Ewing, 1979; Maynard Smith & Hoekstra, 1980). Much less progress was attained for multilocus systems, due to technical difficulties. Consequently, several attempts were undertaken to analyse the multilocus problem under some simplified conditions. These include the assumptions of weak selection and/or loose linkage between the selected loci leading to negligible linkage disequilibria. It was found that under these circumstances, varying optimum of the selected trait does not affect the amount of the maintained genetic variation (Lande, 1976). The same assumption of no linkage disequilibria, considered within the framework of the SAS-CFF model (Gillespie, 1978) of genotype-environmental interaction allows to show the possibility of polymorphism maintenance (Gillespie & Turelli, 1989).

Our recent studies address this problem when no limitation of loose linkage or weak selection is accepted (Kirzhner *et al.*, 1995a; Korol *et al.*, 1994, 1996). It was shown that stabilizing selection with cyclically moving optimum may produce abundant polymorphisms when the selected trait is controlled by additive loci with non-equal effects or by semidominant loci. Moreover, the fact of polymorphism maintenance for non-equal loci appeared to be true for cyclical selection of two-locus haploid systems (Kirzhner *et al.*, 1995a) where constant selection was proved to lead to fixation (Rutschman, 1994). Likewise, in our diploid cyclical selection models, numerous examples were found where polymorphism maintenance under cyclical selection regime is not a phenomenon reminiscent of the constant environment (Korol *et al.*, 1996).

Clearly, environmentally determined cyclical selection may result in fixation or in forced oscillation of the population genetic structure with a period equal to that of the environmental changes. In this paper we report an abundance of additional modes of behaviour manifested by multilocus systems subjected to cyclical selection: (a) supercycles (autooscillations, with a period comprising sometimes dozens or hundreds of external periods), and (b) more complex limiting behaviour (a broad spectrum of chaotic-like trajectories). Classical population genetic models resulting in complex behaviour include, as a rule, some forms of frequency- or density-dependent selection (May & Anderson, 1983; Preygel & Korol, 1990; Altenberg, 1991; Korol *et al.*, 1994). These models directly or indirectly involve an ecological component. By contrast, in our current model of cyclical selection the coefficients in the evolutionary operator do not depend on the systems' phase variables. The selection model considered in this paper is a standard one in population genetics (e.g. Hastings & Hom, 1990; Nagylaki, 1992; Maynard Smith, 1988). Nevertheless, it manifests *en mass* earlier undetected complex dynamic patterns.

Constant selection at single locus level, as well as multilocus selection-free regimes, cannot produce by themselves complex limiting population genetic behaviour (CLB) with an attracting set of a trajectory consisting of more than one point (Geiringer, 1949; Lyubich, 1971; Kirzhner & Lyubich, 1974; Lyubich *et al.*, 1976; Lyubich, 1992). In a continuous two-locus model of constant selection, Akin (1983) found some domains of parameter values which can result in autooscillations. Hastings (1981) constructed an example demonstrating CLB in a two locus discrete-time model. Thus, constant selection can produce CLB in population genetic systems, but only in exceptional cases.

As compared to our recent results (Kirzhner *et al.*, 1996), we describe here a rather wide spectrum of systems with cyclical selection that manifest CLB. These include: haploid and diploid selection for non-equal additive loci, diploid selection for semi-dominant loci including environmental-independent dominance and dominance mode dependent on environment [like in the spatial model of Gillespie (1978)], and several types of genomic distribution of selected loci (a block of tightly linked loci, several such unlinked blocks, and a series of independently segregating loci). Altogether, the analysed examples include systems from three to six loci. All these systems appeared to manifest abundant CLB for a range of the model parameters (recombination rates, individual effects of the involved loci on the selected trait, and dominance effects of the selected loci). Nevertheless, not all combinations of the foregoing types did so (e.g. no such example was found with haploid selection for four unlinked loci). The availability of a broad spectrum of systems manifesting CLB allowed us to check whether these systems share some common features not characteristic in those which do not manifest such behaviour. Although we are quite far from a comprehensive answer to this question, two features may be mentioned here: strong selection and substantial linkage disequilibria. Two features which were exactly opposite to these were assumed in the first multilocus models with temporarily fluctuating environments (e.g. Lande, 1976; Gillespie & Turelli, 1989).

Due to the environmental initiative of the revealed unusual dynamic patterns, it was of primary interest to check whether CLBs are robust to disturbances in the parameters characterizing the environmental variation, e.g. of the optimal values of the selected trait along the period, or the period length. The answer is positive, that is, the revealed supercyclical movements are, to some extent, resistant to such disturbances. We also answer positively to another related question, concerning resistance of CLB to random drift: the simulations showed that to a certain extent CLBs are robust to fluctuations caused by finite population size,

The results of this research program reveal a new broad class of relatively simple genetic systems manifesting extremely complex dynamic patterns. This may have important consequences for evolutionary theory, showing that complex behaviour may arise even in single species genetic systems without frequency and/or density dependent selection. In particular, this precludes any attempts to find the "target" for multilocus cyclical selection (optimization criterion) for any pattern of genomic distribution of the selected loci (i.e. the existence of CLB means non-existence of a global Lyapunov function even when calculated over periods).

The biological relevance of the findings presented in this paper depends on (i) how real the parameter sets are which result in CLB, and (ii) whether the required strength of selection and resulting mean fitness are compatible with the reproductive capabilities of real populations. Both questions can be answered positively. The range of ratios of gene effects, dominance ratios, and rates of recombination in our numerical examples seem to be quite realistic.

More complex is the question of mean fitness. It appeared that in case of purely additive non-equal genes, very low mean fitness is characteristic of the complex trajectories. However, in case of dominant gene action, a significant part of situations with CLB lies in the fitness range of 0.1–0.3. Moreover, for the class of more realistic models, with the selected trait being controlled by semidominant genes with non-equal effects, it is easy to find CLB regimes with rather high mean fitness, up to 0.4–0.6, which is compatible even with the relatively low reproductive capacities of many reptiles, birds, and mammals, let alone organismal groups with higher reproduction rates, i.e. most living organisms. An example of a supercycle with quite a high mean fitness (at any generation) is provided in Fig. 7(a). Here the mean

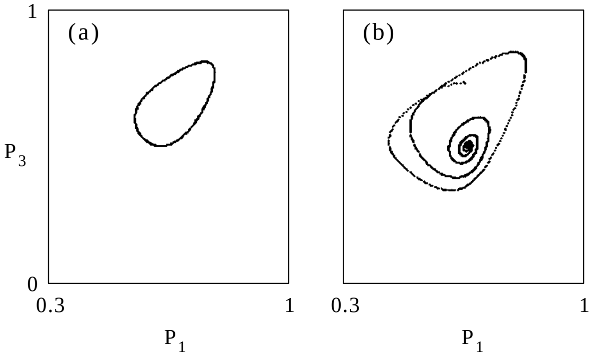

FIG. 7. Supercycle caused by cyclical diploid selection for a trait controlled by four linked semidominant loci with unequal effects. (a) Stable supercyclical autooscillations in the system with $r = 0.005$; $s = 0.40$, $d_1 = 0.1$, $d_2 = 0.2$, $d_3 = 0.3$, $d_4 = 0.4$; $h_1 = 0$, $h_2 = 1$, $h_3 = 0$, $h_4 = 1$, $n_1 = n_3 = 1$, $n_3 = 0$, $z_1 = 0.75$, $z_3 = -0.005$. (b) Damping oscillations (convergence to a polymorphic fixed point) in the same system with no recombination ($r = 0$). The spectrum of linear approximation at this fixed point includes a complex eigenvalue $0.9977 \pm 0.0445i$, that corresponds to oscillations with a period of about 140 units (environmental cycles) whereas the observed period [see Fig. 7(a)] was about 170 units.

fitness along the whole supercycle varies in the range 0.39–0.41 at either of the environmental stages. Corresponding changes in linkage disequilibrium D'_{ij} [scaled on products of allele frequencies $(p_i q_i p_j q_j)^{1/2}$, where p_m and q_m are allele frequencies at mth locus $(m = i, j)$] are of interest. For a four-locus situation one may consider 6 D's, but we present only those for neighbouring loci, D'_{12}, D'_{23}, D'_{34}. In the foregoing example, the range of variation of these coefficients was: (a) in state 1: 0.01–0.01, 0.52–0.68, and 0.27–0.50, respectively, and (b) in state 2: 0.07–0.33, 0.34–0.57, and 0.43–0.60.

Ford (1971) was among the first who demonstrated that strong selection may be a common phenomenon in nature. Moreover, the whole concept of the evolution of co-adapted blocks of genes is based on the assumption that strong selection and tight linkage are the major factors maintaining these blocks intact (e.g. Darlington, 1971). Many examples of polymorphic co-adapted gene blocks are well known [reviewed in Ford (1971), Darlington (1971), Clegg *et al.* (1978) and Korol *et al.* (1994)]. Clearly, if the question is the polymorphism maintenance itself, the requirements to the stringency of selection can be significantly reduced [see an example of cyclical selection on p. 1438 in Korol *et al.* (1996), where the geometric mean fitness was $W = 0.80$, with a nearly global stability of the polymorphism]. The number of such examples can easily be increased. However, if the question is preservation of linkage disequilibrium in a polymorphic population, then higher selection intensities are generally required. And finally, existence of polymorphism in the form of CLB requires an even stronger selection. As we could see from the presented examples of CLB [e.g. Fig. 1(a), (b) and (e)], varying along the trajectories linkage disequilibrium is a characteristic feature of CLB. It is noteworthy, that in case of non-equal linked loci [Fig. 1(a)] the highest disequilibria are characteristic to strongest loci; this note is also true for the case of two unlinked blocks [Fig. 1(e)]. It is also worth mentioning the existence of linkage disequilibrium between the unlinked blocks.

The revealed phenomenon of complex limiting behaviour caused by simple cyclical selection might be considered a novel evolutionary mechanism that can assist, in combination with mutation, in long-term maintenance of genetic variation. Thus, it can substantially contribute to the standing biodiversity over evolutionary time.

The useful comments and suggestions of the referees are acknowledged with thanks. This work was supported by the Israeli Ministry of Science, Israeli Ministry of Absorption, the Israel Discount Bank Chair of Evolutionary Biology, and the Ancell-Teicher Research Foundation for Genetics and Molecular Evolution.

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