Dynamics of recombination modifiers caused by cyclical selection: Interaction of forced and auto-oscillations

A. B. KOROL*, V. M. KIRZHNER AND E. NEVO

Institute of Evolution, University of Haifa, Haifa 31905, Israel

(*Received 12 September 1997 and in revised form 3 March 1998 and 1 June 1998*)

Summary

Temporally varying selection is considered to be one of the potential mechanisms of recombination evolution. We found earlier that simple cyclical selection for a trait controlled by multiple additive, dominant or semi-dominant loci can result in extremely complex limiting behaviour (CLB) of population trajectories, including 'supercycles' and more complex attractors. Recombination rate proved to be a key factor affecting the mode of CLB and the very existence of CLB. Therefore, we considered here a generalized model: the fixed recombination rate was replaced by a polymorphic recombination modifier. The modifier-dependent changes included: (a) supercyclical dynamics due to the recombination modifier in a system that does not manifest CLB when recombination rate is a fixed parameter; (b) appearance of a new level of superoscillations (super-supercycles) in a system that manifests supercycles with a fixed modifier; (c) chaotization of the regular supercyclical dynamics. The domain of attraction of these movements appeared to be quite large. It is noteworthy that the modifier locus is an active participant in the observed non-monotonic limiting movements. Interactions between short-period forced oscillations and the revealed long-period auto-oscillations appeared to result in new regimes of recombination evolution (for some range of linkage between the modifier locus and the selected system), as compared with those caused by the forced oscillations alone.

1. Introduction

The evolution of recombination remains an important unsolved problem in evolutionary genetics. The results of experiments on artificial selection for altered recombination rates (r) suggest that almost every population has enough stored genetic variability to ensure response to selection for changed r (reviewed in Brooks, 1988; Korol *et al.*, 1994). Theoretical analysis shows that under stable environmental conditions a panmictic population polymorphic for fitness-related loci should evolve towards the minimum possible level of recombination. Namely, introduction of a new modifier allele affecting r into an equilibrium polymorphic population is accompanied by an increase in its frequency if it reduces r (Zhivotovski *et al.*, 1994; Barton, 1995). Hence, factors should exist opposing this trend. Moreover, there is some evidence for a possible negative correlation between an individual's

fitness and the level of meiotic recombination in the same individual (Zhuchenko & Korol, 1985; Zhuchenko *et al.*, 1986; Cvetkovic & Tucic, 1986). This implies that the problem of identifying factors ensuring the maintenance of non-zero (and/or polymorphic) recombination within natural populations is even more complicated than anticipated.

A series of models have been proposed to explain the evolutionary mechanisms responsible for the persistence of recombination (and sex in general) in nature. These include selection in variable abiotic conditions, selection against harmful mutations and frequency-dependent selection caused by interaction between antagonistic species (for reviews and classifications of the models see: Maynard Smith, 1988*a*; Kondrashov, 1993; Korol *et al.*, 1994; Otto & Michalakis, 1998). The basis of these models is the assumption that the gene pool is subjected to variable conditions (either external, due to changes in the selection regime, or internal, due to the mutation process). Previous theoretical studies have shown that

* Corresponding author. Telephone: (972) 4240 448. Fax: (972) 4246 554. e-mail: korol@esti.haifa.ac.il.

temporal environmental variation can indeed promote increased recombination, although the revealed patterns appear to be very complex (Charlesworth, 1976, 1993; Maynard Smith, 1980, 1988*b*; Sasaki & Iwasa, 1987; Bergman & Feldman, 1990; Barton, 1995; Korol & Preygel, 1989; Korol *et al.*, 1994; Kondrashov & Yampolsky, 1996; Feldman *et al.*, 1997). A few experimental studies and observations have shown that selection for adaptively important traits may indeed result in changes in the recombination system, e.g. in an increased rate of recombination (Flexon & Rodell, 1982; Burt & Bell, 1987; Wolf *et al.*, 1987; Gorodetsky *et al.*, 1990; Gorlov *et al.*, 1992; Korol & Iliady, 1994; Derzhavets *et al.*, 1996; Saleem *et al.*, 1998).

A Mendelian population subjected to a strictly cyclical selection regime is expected to manifest one of the following two modes of dynamics at the selected loci: (1) stable forced oscillations for all loci, with a period equal to that of the environment (Korol *et al.*, 1996); or (2) fixation for some or all of the loci. Taking any point within the period as a 'phase point', we can refer to the first situation as 'stable polymorphism' and to the second as 'fixation'. In other words, by considering the time scale in terms of environmental periods, the first case could be trivially classified as a *polymorphic stable point* (Kirzhner *et al.*, 1995*a*). We have shown earlier that simple cyclical selection for a trait controlled by multiple additive, dominant or semi-dominant loci can result in extremely complex limiting behaviour (CLB) of diploid and haploid population trajectories (Kirzhner *et al.*, 1996, 1998*a*, *b*). Such behaviour was observed for a broad range of system parameters.

The foregoing studies have shown that recombination rate strongly affects the mode of CLB and the existence of CLB. Therefore, it should be both interesting and instructive to analyse how this phenomenon will be expressed when, instead of a fixed parameter *r*, the rate of recombination is a genetically controlled trait, dependent on a polymorphic modifier ('*rec*-modifier'). A stronger motivation to analyse such models comes from the general interest in the evolution of sex and recombination. Indeed, the foregoing results on CLB were obtained with *standard* models of stabilizing selection with a cyclically moving optimum – exactly the same models that have been employed in models of recombination evolution in changing environments (Maynard Smith, 1980, 1988*a*; Korol & Preygel, 1989; Charlesworth, 1993; Korol *et al.*, 1994; Barton, 1995).

We have previously analysed the effect of a *rec*-modifier on the behaviour of a two-locus population with a special fitness matrix that manifested super-cyclical oscillations with a very long period (Kirzhner *et al.*, 1995*b*). Introduction of a polymorphic modifier resulted in the emergence of a higher level of oscillations (referred to as '*super-supercycles*'). That is, the modifier itself manifested some cyclical behaviour, such that the full period of the modifier trajectory consists of many dozens or even hundreds of supercycles. With respect to the forces affecting modifier dynamics in CLB systems, one should take into account the following factors: short-period environmental oscillations causing a corresponding movement of haplotype and allele frequencies, super-cyclical auto-oscillations with a long period (as a rule), and the linkage of the modifier to the selected system.

This approach is applied here to our standard CLB models based on cyclical selection for a trait controlled by multiple additive, dominant or semi-dominant loci (see Kirzhner *et al.*, 1996, 1998*b*). We analyse the dynamics of multilocus systems with polymorphic *rec*-modifiers subjected to cyclical selection. The parameter sets are chosen in such a way that the selected system manifests relatively simple modes of CLB (supercycles) or a stable polymorphism (in the sense explained above). Different types of *rec*-modifiers will be considered: (1) modifiers of recombination in all intervals of a chromosome; (2) modifiers with a non-even distribution of the effects, including: (i) modification of linkage between blocks of tightly linked loci, with no effect on the within-block recombination; and (ii) modification of linkage within blocks, with no effect on recombination between the blocks.

2. The model

We examine the behaviour of an infinite population with panmixia, non-overlapping generations and several diallelic loci, A_i/a_i ($i = 1, \ldots, L$), affecting the selected trait, u, plus a modifier M/m which is neutral with respect to u but affects the rate of recombination between A_i/a_i. Consider a genotype g with $u = u(g)$ defined as: $u(g) = \Sigma_i u_i(g)$, where the effect of the *i*th locus of genotype g is specified as:

$$u_i(g) = \begin{cases} d_i, & \text{for } A_i A_i \ (d_i > 0), \\ d_i(1+h_i)/2, & \text{for } A_i a_i \ (-1 \leqslant h_i \leqslant 1), \\ 0, & \text{for } a_i a_i. \end{cases}$$

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

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

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

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

$$x'_m = \Sigma w_t(u(g_{ij})) P_{ij,m} x_i x_j / W, \qquad (1)$$

where x and x' are gamete frequencies in adjacent generations; W is the mean fitness; and $P_{ij,m} \geqslant 0$ is the probability of producing gamete m by a genotype g_{ij} resulting from the union of gametes i and j, $\Sigma P_{ij,m} = 1$. 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}. Clearly, $P_{ij,m}$ depends on the recombination parameters, determined by the modifier locus. Computer modelling was based on iterations of (1) for $L+1$ loci (L selected and the modifier).
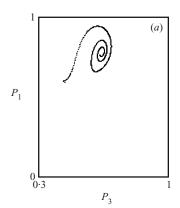
3. Results

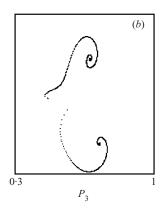### (i) *Modification of recombination rates in all intervals*

For the sake of simplicity, let us assume equidistant distribution of the selected loci in the chromosome, and equal effects of the modifier locus on recombination in each interval. We consider here a special mode of CLB of the selected system – supercycles – as a basis for analysing the complications caused by the introduction of a polymorphic modifier into the system. The usual way to study the fate of the modifier locus, especially when using analytical tools, is to introduce at a low frequency a new modifier allele after reaching a (polymorphic) steady state for the selected system (Feldman *et al.*, 1997). We are interested in following the full dynamics; hence starting the trajectories at arbitrary polymorphic initial points allows us to evaluate the volume of the CLB attraction domain. Three quite different types of *rec*-modifier effects on CLB will be demonstrated: (a) modifiers as the source of CLB; (b) modifiers as a source of the 'next level' of CLB (super-supercycles); (c) modifiers as a factor in the chaotization of population dynamics.

(a) *Modifiers as the source of CLB*

The major part of the results in this paper concerns the mode of modifier evolution as dependent on the system dynamics, referred to as CLB. Therefore, the existence of CLB in the system with a fixed modifier is the precondition of such a consideration. However, an important question is whether or not the presence of a polymorphic modifier may by itself be the factor producing CLB. In other words, would it be possible to obtain CLB by injection of a new modifier allele into a system that is incapable by itself of manifesting this mode of dynamics at any fixed value of recombination? As an example, consider a model with three slightly dominant loci with non-equal effects on the selected trait, in which no CLB was found in computer simulations at any $0 < r < 0.5$. With a polymorphic modifier ($r_{mm} = 0$, $r_{mM} = 0.05$, and $r_{MM} = 0.5$), the system manifests supercyclical damped oscillations (Fig. 1 a). A slight alteration of the parameters results in similar system behaviour, the only difference being the appearance of a second such
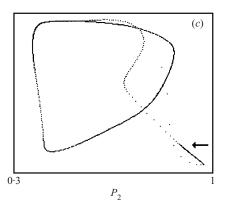

Fig. 1. Modifiers as a cause of supercyclical behaviour. The selected system consists of three additive loci (i.e. $h_i = 0$) with unequal effects. P_i is the frequency of the allele with a positive effect on the trait at locus i. (*a*) Damped oscillations. $d_1 = 1.2$, $d_2 = 2.05$, $d_3 = 4.075$; $s = 1.76$; $r_{mm} = 0$, $r_{Mm} = 0.05$, $r_{MM} = 0.5$; $r_c = 0.1$. The optimum trait values in four environmental states (each continued for one generation, $n_1 = n_2 = n_3 = n_4 = 1$) were $m_1 = 6.78$, $m_2 = 3.76$, $m_3 = 0.1$ and $m_4 = m_2$. (*b*) 'Bistable' damped oscillations (starting from different initial points). $d_1 = 1$, $d_2 = 2$, $d_3 = 4$; $s = 1.75$; $r_{mm} = 0$, $r_{Mm} = 0.05$, $r_{MM} = 0.5$; $r_c = 0.1$. The optimum trait values in four environmental states ($n_1 = n_2 = n_3 = n_4 = 1$) were $m_1 = 6.8$, $m_2 = 3.5$, $m_3 = 0.1$ and $m_4 = m_2$. (*c*) Stable supercycle. The parameters of the model are: $d_1 = 2$, $d_2 = 1.3$, $d_3 = 4$; $s = 1.3$; $r_{MM} = 0.5$, $r_{Mm} = r_{mm} = 0$, $r_c = 0.1$; $n_1 = n_3 = 1$, $n_2 = 0$; $m_1 = 7.1$, $m_3 = 0.05$. The initial part of the trajectory was obtained with the modifier fixed with $r = r_{mm} = 0$. The trajectory converged to a polymorphic stable point marked by the arrow. Then an alternative allele M ($r_{MM} = 0.5$) was injected into the system (with a low initial frequency). The period of the resulting supercycle is about 360 environmental periods.
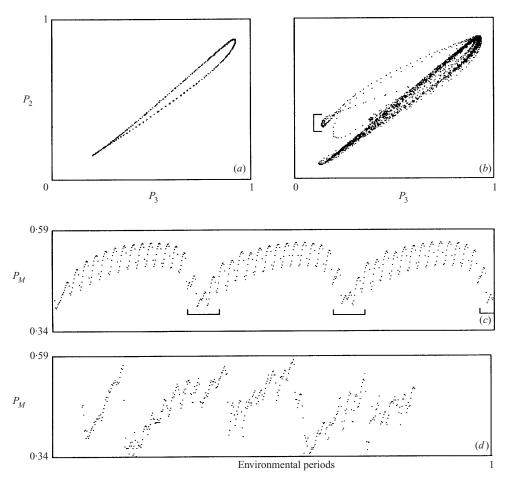
Fig. 2. Super-supercycles, based on interaction of supercyclical dynamics of three semi-dominant selected loci and a polymorphic modifier. The selected system consists of three equal semi-dominant loci ($d_i = 1$), $h_1 = 0.3$, $h_2 = 0.3$, $h_3 = 0.4$; $r_{MM} = 0.02$, $r_{Mm} = r_{mm} = 0$, $r_c = 0.01$; the selected optima were $m_1 = 3.3$ and $m_2 = 0.3$ ($n_1 = n_2 = 1$), $s = 0.84$. (*a*) The phase diagram of the initial supercycle (the modifier is fixed for *MM*); the period of this supercycle is about 60 environmental periods. (*b*) The phase diagram of the system with polymorphic modifier. (*c*) The super-supercyclical dynamics of the modifier (represented across environmental periods). The brackets mark the points of a failure of stability of the basic supercycle caused by the current dynamics at the modifier locus. (*d*) Resistance of the super-supercycle to moderate random disturbances of the environmental period (with a probability of $\pi = 0.1$ along the trajectory, n_1 or n_2 become independently equal to 2).

point, so that two similar movements can be observed. These bistable damped oscillations are presented in Fig. 1*b*.

The third example provides a true supercycle, with non-damped auto-oscillations (Fig. 1*c*), obtained by injection of the modifier allele M ($r_{MM} = 0.5$) into a system that has reached its polymorphic stable point for loci affecting the selected trait (with the modifier locus being fixed for m, $r = r_{mm} = 0$). The attraction domain of the resulting supercycle in the whole phase space of the system is very large. Along the limiting trajectory, the frequency of allele M varies in the range of 0914–0·971; the corresponding range of the mean rate of recombination will be $0.417 < r < 0.471$ (assuming Hardy–Weinberg proportions at the modifier locus). With fixed recombination, for all values of r from this range, the three-locus selected system being considered manifested no complex

behaviour. Moreover, with fixed recombination, the system trajectories go to fixation at any $r > 0.05$. Therefore, the polymorphic modifier not only is the source of complex limiting behaviour; the very existence of (protected) polymorphism at loose linkage between the selected loci is possible here only in the form of CLB, caused by the presence of the polymorphic *rec*-modifier.

(*b*) *Super-supercycles caused by interaction of supercyclical dynamics and modifier movement*

This mode of behaviour arises when a polymorphic *rec*-modifier is introduced into a system that is itself capable of manifesting supercyclical dynamics under some range(s) of the recombination rate. It is a rather trivial fact that the allele frequencies at the modifier locus may oscillate with a period equal to that of the
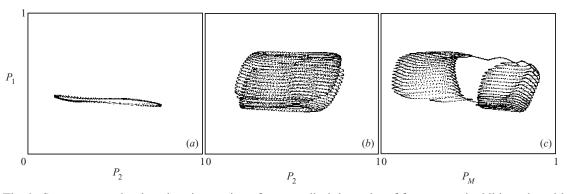
Fig. 3. Super-supercycles, based on interaction of supercyclical dynamics of four unequal additive selected loci and polymorphic modifier. The selected system consists of four unequal additive loci ($h_i = 0$) with $d_1 = 0.01$, $d_2 = 0.04$, $d_3 = 0.16$, $d_4 = 3.4$; only single recombination events were allowed within the chromosome segment containing the selected loci; $r_{MM} = 0.5$, $r_{Mm} = 0.25$, $r_{mm} = 0.01$; the modifier was closely linked to the fourth selected locus, $r_c = 0.0005$; the selected optima $m_1 = 1.1$ and $m_2 = 0$ ($n_1 = n_2 = 1$); $s = 0.17$. (*a*) The supercycle obtained with fixed recombination rate $r = 0.25$. (*b*) The phase diagram of the super-supercycle with a polymorphic modifier. (*c*) Modifier superoscillations consisting of two separate subsets.

supercycle. However, it appears that, in addition to this movement, the modifier locus may manifest auto-oscillations with a much longer period. In turn, the dynamics of the modifier cause long-periodical changes of the supercycle itself. A first example of such dynamics, referred to as 'super-supercycles', was provided in our previous paper (Kirzhner *et al.*, 1995*b*). In that example the model included a modifier of recombination and a two-locus selected system, subjected to cyclical selection with a very special fitness matrix. Here we consider super-supercyclical dynamics based on a more natural class of models: multilocus systems subjected to stabilizing selection with a cyclically moving optimum. Two examples are provided in Figs. 2 and 3. The supercyclical dynamics presented in Fig. 2*a* are robust with respect to changes of recombination rate approximately in the range 0.002–0.04. Let the recombination rate in the system now be dependent on the *rec*-modifier: $r_{mm} = r_{mM} = 0$ and $r_{MM} = 0.02$. Then, given a certain recombination level r_c between the modifier and the selected system ($r_c = 0.01$, in the present example), the super-supercycle shown in Fig. 2*b, c* will be obtained. It can be seen that each large period in Fig. 2*c* consists of about 20 oscillations corresponding to the initial supercycles (i.e. the total period of the modifier is about 1000 environmental periods). The robustness of the revealed pattern to random disturbances of the environmental period is also presented (Fig. 2*d*) and considered in Section 4.

The second example concerns a system with complete positive interference (i.e. only single exchanges were allowed). The initial supercycle here is very simple (Fig. 3*a*). With the polymorphic modifier the behaviour is much more complex. In the example of Fig. 3*b, c* the frequency of crossing-over within the selected system was $r_{mm} = 0.01$, $r_{mM} = 0.25$ and $r_{MM} = 0.5$. As can be seen, the modifier manifests

superoscillations corresponding to those of the selected system. However, this behaviour of the modifier occurs in two rather separate subsets, with transitions between them occurring in the form of short-time jumps (Fig. 3*c*). It is noteworthy that the consequent visits of the two subsets take tens of thousands of generations.

(*c*) *The modifier as a cause of chaotization of population dynamics*

In the example presented in Fig. 4, a fixed re-combination rate resulted in CLB solely in the form of supercycles (and only in the indicated range of *r*). Only simple fixed points were found for *r* values corresponding to *mm* and *MM* states of the modifier (Fig. 4*a*). The situation may change dramatically when the selected system is complemented by a polymorphic *rec*-modifier. For example, coevolution of the modifier and the selected system may result in a complex attractor like that presented in Fig. 4*b*. This example was tested with respect to the sign of the Lyapunov exponent, *L* (Wolf *et al.*, 1985). It appeared that $L \approx 0.04 > 0$, so that the corresponding CLB can be classified as chaotic (Hastings *et al.*, 1993). It is noteworthy that this phenomenon does not mean that any kind of CLB should be characteristic of the system with fixed *r* corresponding to either *mm* or *MM*. However, one may assume that the existence of a range of such *r* values is 'exploited' by the system with polymorphic recombination to produce more complex limiting patterns.

(ii) *Modifiers with an uneven distribution of effects along the chromosome*

We consider two situations: (*a*) modification of linkage between blocks of linked loci, with no effect on
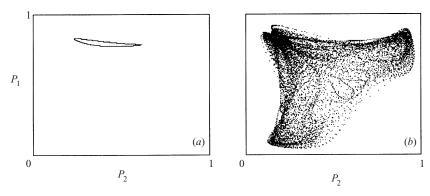
Fig. 4. Transformation of a simple supercyclical dynamics into a complex attractor when a fixed recombination rate (r = const) is replaced by a polymorphic modifier. The selected system consists of three equal semi-dominant loci ($d_i = 1$), $h_1 = h_2 = 0.28$, $h_3 = 0.4$; the optima were $m_1 = 3.0$ and $m_2 = 0$ ($n_1 = n_2 = 1$), $s = 0.95$. (*a*) The phase diagram of a supercycle found in the range of recombination rates $r \approx 0.0001–0.006$ (the example assumes $r = 0.003$). (*b*) The phase diagram of the system with a polymorphic modifier ($r_{MM} = 0.1$, $r_{Mm} = r_{mm} = 0$, $r_c = 0.01$).
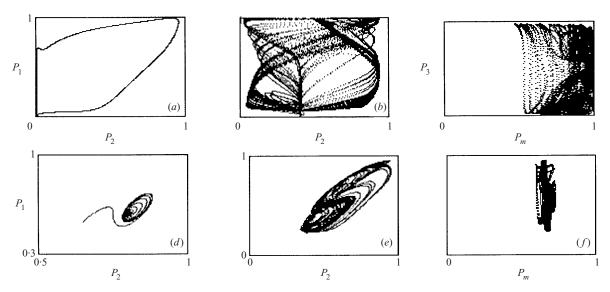

Fig. 5. Complex dynamics with an uneven distribution of the modifier effects along the chromosome. (*a*)–(*c*) Modifier affects recombination between blocks but not within the blocks. The selected system consists of two blocks of linked purely additive loci ($h_i = 0$), {$d_1 = 0.2$ and $d_2 = 0.2$}, {$d_3 = 0.5$ and $d_4 = 1$}, $s = 0.25$, $r_w = 0.1$, $m_1 = 1.65$, $m_2 = 0.2$ ($n_1 = n_2 = 1$). (*a*) Fixed recombination rate between the blocks $r = 0.0001$ (we found cyclical behaviour of the system at $0 \leqslant r \leqslant 0.42$). (*b*) and (*c*) $r_{MM} = 0.5$, $r_{Mm} = r_{mm} = 0.1$; $r_c = 0.01$. (*d*)–(*f*) Modifier affects recombination within the blocks but not between the blocks. The selected system consists of two blocks of linked loci {$d_1 = 1.8$, $h_1 = 0.3$; $d_2 = 1.0$, $h_2 = -0.7$} and {$d_3 = 1.0$, $h_3 = -0.69$; $d_4 = 1.8$, $h_4 = 0.32$}, recombination between the blocks $r_b = 0.3$, $m_1 = 6.055$, $m_2 = 0.1$ ($n_1 = n_2 = 1$), $s = 2.01$. (*d*) Fixed recombination rate within the blocks $r = 0.001$. (*e*) and (*f*) $r_{MM} = 0.02$, $r_{Mm} = r_{mm} = 0$; $r_c = 0.01$ is the distance between the modifier and the fourth selected locus.

recombination within blocks; and (b) modification of linkage within blocks of tightly linked loci, with no effect on recombination between blocks.

(*a*) *Modification of linkage between blocks of linked loci, with no effect on recombination within blocks*

In the example presented in Fig. 5*a*–*c* the selected system consists of purely additive loci with unequal effects and the modifier is linked to the locus with the strongest effect on the selected trait. The resulting CLB (Fig. 5*b*, *c*) was classified as a chaotic attractor, because the Lyapunov exponent is definitely positive here ($L \sim 0.01$) and initially close starting points produce divergent trajectories. We have also considered the same selected system with the modifier linked to the selected locus with smallest effect. Clearly, these situations are not equivalent: the rate of change of the strongest locus is higher than that of weaker loci, which may seriously affect the system dynamics because of 'inertia-like' effects caused by

linkage between the modifier and the selected loci (Kirzhner *et al.*, 1995*b*; see also Section 4). Indeed, the resulting attractor manifested much simpler dynamics (a super-supercycle with $L = 0$; not shown).

(*b*) *Modification of linkage within blocks of tightly linked loci, with no effect on recombination between blocks*

This situation of recombination modification is complementary to that considered in the previous section, where the modifier controlled the recombination rates between blocks but had no effect on within-block recombination. The difference between configurations when the modifier is closer to the locus with the strongest or, conversely, the smallest effect, was stressed there. The structures of the systems considered in the current section allow for a further complication of the 'genetic inertia' effects. Our initial motivation was in fact to consider such structures. Indeed, the fate of a genetic modifier, including a modifier of recombination, may strongly depend on its linkage to the selected loci (see Section 4). The proposed structures provide an interesting opportunity to analyse the behaviour of the modifier and the whole system when two contrasting versions of modifier linkage to the selected blocks exist simultaneously in the system, i.e. linked and freely recombining. Note that from the viewpoint of recombination evolution modelling, this type of system is much more realistic than multilocus systems with one linkage group: it is natural to assume that loci affecting fitness-related quantitative traits are spread over more than one locality of a multichromosomal genome (Lewontin, 1974; Korol *et al.*, 1994). It also fits the concept and corresponding evidence for 'fine' control of recombination (Simchen & Stamberg, 1969; Chinnici, 1971). In the example presented (Fig. 5*d–f*), with two unlinked blocks, only damped superoscillations were observed for the phase variables with fixed recombination (at $r = 0.014$). In the system polymorphic for the *rec*-modifier, the complex dynamics become stable (Fig. 5*e, f*).

4. Discussion

(i) *The phenomenon*

We have shown earlier that simple cyclical selection for a trait controlled by multiple additive, dominant or semi-dominant loci can result in extremely complex limiting behaviour (CLB) of diploid population trajectories (Kirzhner *et al.*, 1996, 1998*a, b*). The recombination rate proved to be a key factor affecting the mode of CLB and the existence of CLB. Therefore, we have considered here a generalized and more

natural model: the fixed recombination rate was replaced by a polymorphic recombination modifier. The effect of such a replacement on CLB has already been analysed for a more specialized two-locus system (Kirzhner *et al.*, 1995*b*).

Several types of *rec*-modifiers were considered in this paper: (1) modification of recombination rates in all intervals of a chromosome; (2) modifiers with an uneven distribution of effects, including modification of linkage between blocks of linked loci, with no within-block effect, and modification of linkage within blocks of tightly linked loci, with no between-block effect. The modifier-dependent changes included: (a) supercyclical dynamics due to the *rec*-modifier in a system that does not manifest CLB when recombination rate is a fixed parameter; (b) the appearance of a new level of superoscillations (super-supercycles) in a system that manifests supercycles under fixed modifier; (c) chaotization of the regular supercyclical dynamics. While the attractors of the first two types seem to be rather complex, trajectories starting from neighbouring initial points do not diverge. Moreover, the domain of attraction of these movements appeared to be quite large, sometimes manifesting a nearly global stability. To a large extent this phenomenon is due to polymorphism at the modifier locus. Namely, with fixed r at the level corresponding to CLB for the selected system itself, if CLB exists at all in such a case, the CLB-attracting domain in corresponding phase space may be smaller. This effect was also observed in our former study of CLB with polymorphic *rec*-modifier for a more specialized regime of cyclical selection (Kirzhner *et al.*, 1995*b*). It is noteworthy that the modifier locus is an active participant in the observed complex non-monotonic limiting movements, although its dynamics may have some specific components that differ from those of the selected loci (e.g. Figs 2, 3).

An important aspect characterizing the described pattern is its *robustness* with respect to changes in the parameters. In general, this question could be addressed in relation to the dynamics of the selected system with either fixed or polymorphic recombination. We have recently shown (Kirzhner *et al.*, 1998*b*) that, with a fixed recombination rate, CLB may be quite a robust phenomenon, resistant to variation in parameters characterizing: (i) the effect of the selected loci (d_i and h_i); (ii) the rate of recombination; (iii) the intensity of selection; (iv) the optima for the trait; (v) random disturbances in the period length and optima; and (vi) random fluctuations of haplotype frequencies due to drift (caused by finite population size). These results are also true for CLB patterns manifested by population models with polymorphic recombination modifiers. In particular, all the examples provided in Figs. 1–5 manifest CLB not only with the parameter values

provided in the legends, but also over some range of these parameters. For instance, the system of three purely additive selected loci of non-equal effects in Fig. 1 *c*, where the modifier locus is the source of CLB, manifests the observed pattern not only for the values of d_1–d_3 presented, but also for a range of independently varying values of d_i ($i = 1, 2, 3$) (up to about 10 % for d_1 and d_2 and 2–3 % for d_3; not shown). Another example is a system of three equidistant selected loci of equal effects $d_1 = d_2 = d_3 = 1$, period $p = n_1 + n_2 = 1 + 1$ with optima $m_1 = 3.2$ and $m_2 = 0.2$ and $s = 1.1$. At fixed recombination rate (in the range 0–0.01) this system manifests either supercyclical auto-oscillations or convergence to a fixed point for any h_i ($i = 1, 2, 3$) from the interval [0.06–0.12]. With a polymorphic modifier ($r_{MM} = 0.01$, $r_{Mm} = r_{mm} = 0$; $r_c = 0.001$), we observed more complex, chaotic-like dynamics for any combination of h_i values taken independently from the foregoing range [0.06–0.12].

The phenomenon of super-supercycles appeared to be qualitatively resistant to moderate random disturbances of the environmental period. In the model presented in Fig. 2, the period structure of the initial process was $n_1 = n_2 = 1$. In the disturbed process, with a probability of π along the trajectory, n_1 or n_2 become independently equal to 2. One can easily see (compare Fig. 2 *c* and 2 *d*) that the supercyclical mode of the dynamics is preserved at least for $\pi = 0.1$.

(ii) *Proposed mechanism*

How can the innate ability to generate supercycles affect the fate of modifiers in the population? To explain the observed phenomenon of a further complication of CLB with the introduction of a polymorphic *rec*-modifier (birth of a super-supercycle in a system already manifesting super-auto-oscillation), we proposed earlier a new notion of 'genetic hysteresis' (Kirzhner *et al.*, 1995 *b*). This reflects the fact that, under super-supercyclical movement, the characteristics of the system dynamics depend not only on the position of the system's coordinates in the phase space, but also on the direction of this movement (e.g. whether the frequency of an allele for higher recombination rate is increasing or decreasing over the specific part of the trajectory). Linkage of the modifier locus to the selected system, a kind of an 'inertia factor', proved to be the key component determining the main characteristics or even the very possibility of such a pattern.

For different types of genetic modifiers, it is known that the mode of modifier dynamics and the evolutionary stable level of the modified parameter (e.g. the rate of recombination or mutation) can critically depend on its linkage to the selected system (reviewed in Korol *et al.*, 1994; Feldman *et al.*, 1997). As regards a *rec*-modifier, the general conclusion is that close linkage promotes a more rapid spread of the allele enhancing recombination. In a model with a varying environment, Charlesworth (1976) observed an increased rate of the recombination-enhancing allele when the modifier was linked to the selected loci. He has also established that, for long periods of environmental fluctuation, situations are possible when the intensity of linkage of the modifier with the selected loci affects not only the rate but also the direction of its dynamics. If the modifier is unlinked to the selected loci then the recombination-enhancing *rec* allele is eliminated from the population, and if it is linked then it becomes established. The same effect was observed in a selection–mutation balance model (Feldman *et al.*, 1980). An increase in the equilibrium recombination value with a closer linkage of the *rec* locus with the selected system has also been reported for a haploid model with a varying environment (Sasaki & Iwasa, 1987). It is generally assumed, probably under the influence of the above results, that linkage enhances the intensity of selection for increased recombination (Brooks, 1988). However, our previous results showed that an opposite trend may be characteristic of cyclical selection with short period (Korol *et al.*, 1990, 1994). In such a situation selection for increased *r* is most effective when the *rec* locus is unlinked or loosely linked to the selected system. Tighter linkage *can alter the direction of change*, resulting in the fixation of the allele reducing recombination. With a longer oscillation period, i.e. with a more stable environment, intermediate linkage is optimal in terms of selection for increased *r*. Finally, in a still more stable environment with long periods of constant conditions, selection for recombination is most effective under tight linkage (see Korol *et al.*, 1994, pp. 208–12). Table 1 illustrates this effect for a situation when the selected trait depends on three tightly linked loci. Similar results were obtained also for multilocus selection in host–parasite systems (Preygel & Korol, 1990; Korol *et al.*, 1994, p. 250; but for mutation modification in such systems see Haraguchi & Sasaki, 1996). One could easily see the opposite effects of the intensity of linkage between the modifier and the selected loci on the modifier dynamics for long- and short-period selection regimes.

The consideration of modifier linkage to the selected loci allows us to suggest a simple heuristic explanation of the effects of the modifier on CLB. For that, we should recall first the 'low-pass filter effect' described for evolution of modifiers of recombination rate (Sasaki & Iwasa, 1987) and mutation modifiers (Ishii *et al.*, 1989). It was found that in a system subjected to fluctuating selection with a mixture of oscillations with different period lengths, the fate of the modifier is determined mainly by the lowest frequency component. In our models, we have two components of

Table 1. *Dynamics of a recombination modifier in a cyclically varying environment as a function of linkage between the modifier and the selected system*

Period length $p = n_1 + n_2 + n_3 + n_4$	r_c	$P_M^0 \rightarrow$	M is recessive		M is additive	
			0·050	0·950	0·050	0·950
System 1						
$4 = 1+1+1+1$	0·01		0·023	0·057	0·000 (440)	0·001
	0·05		0·030	0·101	0·000 (717)	0·046
	0·1		0·034	0·228	0·001	0·383
	0·2		0·043	0·680	0·012	0·849
	0·5		0·056	0·990	0·134	0·977
System 2						
$40 = 19+1+19+1$	0·01		0·035	0·143	0·004	0·143
	0·05		0·055	0·903	0·121	0·942
	0·1		0·061	0·988	0·217	0·976
	0·2		0·053	0·963	0·077	0·956
	0·5		0·046	0·854	0·021	0·911
$80 = 39+1+39+1$	0·01		0·999	1·000 (721)	1·000 (645)	1·000 (721)
	0·05		1·000 (382)	1·000 (118)	1·000 (461)	1·000 (118)
	0·1		1·000 (715)	1·000 (173)	1·000 (871)	1·000 (173)
	0·2		0·152	0·999	1·000 (723)	0·999
	0·5		0·040	0·412	0·004	0·412

The selected system (three equidistant loci) was allowed to reach equilibrium with fixed recombination at $P_M = 0$ or $P_m = 0$ (with haplotype frequencies in consecutive periods differing by less than 10^{-9} for any moment along the period). Then, the alternative modifier allele was injected at a small frequency (0·05) and with no linkage disequilibria relative to selected loci. The frequency of the M allele after 1000 periods (or the number of periods needed to achieve fixation at the modifier locus, indicated in parentheses) was used to assess how the level of recombination r_c between the modifier and selected system affects dynamics. System 1: $d_1 = d_2 = 1$, $d_3 = 2$, $h_1 = h_2 = 0$, $h_3 = 0·8$; $m_1 = 9$, $m_2 = m_4 = 1$ and $m_3 = 0$, $s = 3$; system 2: $d_1 = d_2 = d_3 = 1$, $h_1 = h_2 = h_3 = 0·6$; $m_1 = 3·2$, $m_2 = m_4 = 2·7$ and $m_3 = 2·0$, $s = 1·5$; in both systems, $r_{MM} = 0·01$ and $r_{mm} = 0$.

the selected system dynamics: (i) forced oscillations with a short period caused by strong-to-moderate cyclical selection; and (ii) low-frequency movements (e.g. supercycles consisting of hundreds or even thousands of environmental periods). Under close linkage of the modifier to the selected system, the first component promotes selection towards lower recombination whereas the second component induces selection for higher recombination alleles (Korol *et al.*, 1990, 1994). In contrast, under moderate or loose linkage the first component may result in increased recombination while the outcome of low-frequency oscillations will be reduced recombination (Charlesworth, 1976). Thus, the effects of oscillations of very low and very high frequencies on the modifier are opposite. According to the principle of Sasaki & Iwasa (1987), in such conditions the fate of the recombination modifier should depend mainly on the second (low-frequency) component. However, along the trajectory, the modifier itself is evolving, which may result in a reduction of the 'current' amplitude of the low-frequency movement. On such intervals of system trajectory, the high-frequency component determines the dynamics of the modifier, preparing the conditions for the next phase. Such a dynamic balance may generate different modes of limiting behaviour considered in the foregoing examples.

To demonstrate that this mechanism is relevant to our system with recombination evolution directed simultaneously by short-period forced oscillations and long-period auto-oscillations, the following artificial construction was considered. The observed auto-oscillatory long-periodical movement was replaced by 'external' long-periodical changes in the selected optimum, so that the cyclical selection regime is composed of high- and low-frequency oscillations (Fig. 6). The short period was determined by alternation of the optima m_1 and m_2 ($n_1 = n_2 = 1$, i.e. short period length was $p = 2$). Slow oscillations ($p = 40$) were simulated by changing the optima according to $m_1 = 3·0\{1 + \sin[2\pi t/40]/3\}$ and $m_2 = 0·3\{1 + \sin[2\pi t/40]/3\}$, where t denotes 'time' along the trajectory measured as the number of short periods passed. In this example, the modifier is closely linked to the selected system ($r_c = 0·05$), hence the allele of higher recombination goes to extinction if the system is subjected only to short period ($p = 2$) selection (not shown). The same result was obtained when the short period was complemented by long-term oscillations (each including 20 short periods). The direction of the modifier dynamics is opposite if the long-term period includes 40 short periods. At $r = r_{mm} = 0$ the selected systems subjected to the two-component forced oscillations converges to the at-
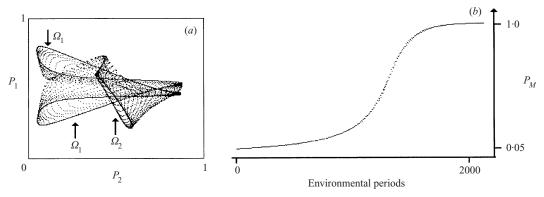
Fig. 6. The effect of a composition of high- and low-frequency forced oscillations on the fate of a recombination modifier closely linked to the selected system. The selected system consists of three equal semi-dominant loci ($d_i = 1$), $h_1 = h_2 = 0.36$, $h_3 = 0.4$, $s = 1.6$; $r_{MM} = 0.01$, $r_{Mm} = r_{mm} = 0$, $r_c = 0.05$. As before, the changes in allele frequencies are shown over the short environmental periods.

tractor Ω (Fig. 6*a*); Ω_1 can be considered an analogue of the supercycle. If allele M is injected at a low frequency (0.05) when the system has reached Ω_1 (after 2000 short periods), then the system will evolve towards a new attractor Ω_2 (Fig. 6*a*) and M goes to fixation (Fig. 6*b*; the moment of injection is denoted here by 0).

How could these 'elementary' processes produce a super-supercycle? For another type of selected system (two-locus cyclical selection defined by alternating of two fitness matrices), we found that such a regime can arise in the vicinity of a fixed polymorphic point if its stability depends on recombination rate (Kirzhner *et al.*, 1995*b*). We believe that this is generally the major factor in the modifier effect on CLB. In principle, if the spectral radius of the linear approximation of the evolutionary operator at this point is close to unity and the maximum eigenvalue is complex, then a cyclical regime is possible (see Kirzhner *et al.*, 1998*b*). Moreover, if the spectral radius varies with the rate of recombination, then the resulting auto-oscillations may undergo a long-term evolution along the trajectory together with and due to the polymorphic recombination modifier. That was precisely the scenario in the model presented in Kirzhner *et al.* (1995*b*). On this basis we can interpret the super-supercyclical behaviour of the model presented in Fig. 4*a*–*c*. For a series of fixed recombination rates (r) the following eigenvalues with maximum module were found:

(1) $r = 0.002$, $\lambda = 1.0173 \pm 0.1333i$, $|\lambda| = 1.026 > 1$;

(2) $r = 0.007$, $\lambda = 1.0092 \pm 0.1299i$, $|\lambda| = 1.017 > 1$;

(3) $r = 0.01$, $\lambda = 0.9908 \pm 0.1158i$, $|\lambda| = 0.9975 < 1$.

Therefore, at $r = 0.01$ slow damping oscillations should arise. At two other values of r stable supercycles are possible and we indeed observed these CLBs. Note

that, in accordance with the spectral radius $|\lambda|$, the amplitude of the supercycle 1 is larger than that of supercycle 2. Let the modifier be polymorphic and closely linked to the selected system ($r_c = 0.01$ in our example). If the initial mean value of r is large enough, then small damping auto-oscillations will arise, promoting evolution towards lower recombination (due to the effect of short forced oscillations and close linkage of the modifier to the selected system, as in the system of Table 1). According to the foregoing spectral properties, the amplitude of the low-frequency auto-oscillations will tend to increase together with the frequency of the allele for low recombination. When this amplitude becomes large enough, it could counter the effect of short forced oscillations and reverse the direction of change of the modifier frequency (like the effects presented in Fig. 6 and Table 1). The reverse dynamics at the modifier (towards increased recombination) will reduce the spectral radius of the fixed point, resulting in a trend of decreasing amplitude of the supercycle, and then the whole process is repeated.

(iii) *Implications for the evolution of recombination*

The two-level auto-oscillations obtained here, caused by (a) reaction of the multilocus system to cyclical selection, and (b) the modifier dynamics, allow us to make some suggestions about the possible role of recombination and sex in complex population dynamics. The majority of results on complex dynamics in population biology come from ecology (for review see Hastings *et al.*, 1993). The main source of complex dynamics patterns in population genetics is frequency-dependent selection in single (Charlesworth, 1971; Roughgarden, 1971; Loeschcke & Christiansen, 1984; Altenberg, 1991) and (mainly) two- or multiple-species interactions (May & Anderson, 1983; Bell & Maynard Smith, 1987; Preygel & Korol, 1990; Hamilton, 1993; Korol *et al.*, 1994; Kirzhner *et al.*,

unpublished data). One of the generalizations derived recently from a study of single-locus ecological-genetic models with restricted mixing was that sex reduces the likelihood of complex dynamics and chaos (Ruxton, 1995, and references therein). This conclusion partially corresponds to our results presented here and in previous papers on cyclical selection (Kirzhner *et al.*, 1996, 1998 *a*, *b*). Sexual reproduction includes two major components: syngamy and meiotic recombination. Our results concern the effect of the second component. The question then is whether more recombination indeed means less complexity. We found that, in general, the appearance of CLB is associated with smaller rates of recombination. However, this dependence is not necessarily a monotonic one; at $r = 0$ CLB is a rare phenomenon (see, for example, the bifurcation diagram in fig. 4 in Kirzhner *et al.*, 1996). Likewise, in some of the examples presented here, the presence of a high recombination allele (e.g. $r_{MM} = 0.5$) was an obligatory condition for a robust manifestation of CLB.

The last question that we would like to discuss is the possible role of the CLB phenomenon in recombination evolution. The described CLB patterns resulted from high-frequency forced oscillations of the optimum value of the fitness-related trait. It is known that in such conditions only very strong selection can provide evolution towards increased recombination (Korol & Preygel, 1989; Korol *et al.*, 1990, 1994; Charlesworth, 1993; Kondrashov & Yampolsky, 1996). The high genetic load needed to promote increased recombination is one of the major difficulties when temporal (cyclical or stoachastic) environmental fluctuations are to be considered as a causal factor (Otto & Michalakis, 1998). Another obstacle is the presumed inability of fluctuating selection to preserve polymorphism, a precondition of recombination evolution (Kondrashov, 1993). We found earlier that this is not really a serious obstacle: stabilizing selection with a cyclically varying optimum for a quantitative trait that depends on purely additive or semi-dominant genes with non-equal effects leads to local polymorphism stability, with a sufficiently large polymorphism attracting domain (Korol *et al.*, 1994, 1996). Analysis of this model shows that the demands for a selection strength sufficient to promote evolution towards increased recombination can be significantly relaxed if the effect of linkage of *rec*-modifier with trait loci is taken into account (Korol *et al.*, unpublished data). For example, the selection regimes for system #2 in Table 1 correspond to geometric mean fitnesses $W = 0.78-0.82$ (although other examples, with $W = 0.85-0.90$, can easily be produced).

The interaction described between short-period forced oscillations and long-period auto-oscillations allows us to propose the following mechanism. The main explanation of the putative role of sex and recombination in a frequently varying stressful environment involves the changing sign of preferred linkage disequilibria (Charlesworth, 1976; Maynard Smith, 1978; Sasaki & Iwasa, 1987; Barton, 1995). For the model of abiotic selection in question, this type of environmental change is very challenging because strong selection is needed to promote recombination. Directed changes or slow periodical variations in the selected optimum are more efficient (Charlesworth, 1993; Barton, 1995). Then increased recombination can become advantageous by facilitating the changes in allele frequencies at selected loci. This mechanism may virtually take place in our CLB dynamics. Indeed, as we can see from the phase diagrams (Figs. 1–5), the supercyclical dynamics was manifested as slow changes of allele frequencies at the selected loci along the trajectory (comprising tens or hundreds of generations). Actually, this means that the mean value of the selected trait can undergo corresponding slow changes. Indeed, in the model of Fig. 2, the mean value of the trait at the environmental state 1 (where the selected optimum was 3·30) varies along the supercycle within the range 1·86–1·98, and at state 2 (selected optimum 0·3) within the range 1·25–1·52, whereas the mean value averaged over the environmental period varied from 1·56 to 1·74. In the model of Fig. 3 we have, correspondingly: 0·28–0·39 for state 1 (selected optimum 0), 0·72–0·82 for state 2 (selected optimum 1·1), and an average over the period of 0·51–0·59. This low-frequency dynamics may favour non-zero (or high) recombination provided there is a close enough linkage of the modifier to trait loci (or to some of them). For example, if the parameter $h_3 = 0.4$ is replaced either by $h_3 = 0.3$ or $h_3 = 0.5$, then stable polymorphism instead of a supercycle will be obtained and the modifier evolves towards zero recombination. The same result will be obtained if $d_3 = 1$ is replaced by either $d_3 = 1.1$ or $d_3 = 0.9$. Therefore, the ability to manifest supercyclical dynamics prevents fixation of the zero recombination allele at the modifier locus. The foregoing effect of low-frequency movements on recombination induced by high-frequency forced oscillations may be important even if it is manifested in an imperfect form, e.g. as damping super-oscillations that can interact with stochastic disturbances of the initial (environmental) period length and selected for optima, finite population size and random mutations. These processes may result in a fixation of a high recombination allele, though the proposed scenario needs further detailed analysis.

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