

# Genetic supercycles caused by cyclical selection

(polymorphism/rec modifier/linkage)

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**ABSTRACT** Typical behavior of a two-locus genetic system experiencing cyclical selection, includes fixation (in one or both loci) or a stable polymorphic cycle with a period equal to that of environmental changes. By considering the time scale in terms of environmental periods, the last case could be trivially classified as a polymorphic stable point. Here we report on some results showing the complex limiting behavior of diploid population trajectories resulting from selection in a cyclically changing environment. We found that simple cyclical selection could produce genetic supercycles composed of many hundreds of environmental periods.

The limiting set of any trajectory of a selection-free panmictic population with Mendelian segregation and recombination could be only a point (1–3). Thus, the Mendelian mechanism cannot produce by itself complex limiting population genetic behavior. Single-locus selection in a constant environment does not change the situation either (4). Hastings (5) suggested an example of a stable cycle resulting from moderate constant selection in a two-locus panmictic population. Such an example for a continuous time model was found by Akin (6). Thus, it has been shown that a constant extrinsic force can produce stable oscillations in population genetic systems. The period of these autooscillations is very long [about 1000 generations in Hastings' results (5)]. Here, we describe a series of different examples that show that autooscillatory behavior (also with a very long period) may arise in systems experiencing high-frequency regular changes of selection coefficients.

## Two-Locus Diallelic Diploid Model

Computer modeling was based on iteration of the standard evolutionary operator for a two-locus diallelic population with panmixia and non-overlapping generations:

$$\begin{aligned} x'_1 &= (W_1x_1 - w_4rD)/W, & x'_2 &= (W_2x_2 + w_4rD)/W, \\ x'_3 &= (W_3x_3 + w_4rD)/W, & x'_4 &= (W_4x_4 - w_4rD)/W, \end{aligned} \quad [1.1]$$

where  $x$  and  $x'$  are haplotype frequencies in consecutive generations;  $r$  is the rate of recombination between the selected loci;  $D$  is the linkage disequilibrium coefficient ( $D = x_1x_4 - x_2x_3$ );  $W_1, \dots, W_4$  are the marginal fitnesses, i.e.,

$$\begin{aligned} W_1 &= w_1x_1 + w_2x_2 + w_3x_3 + w_4x_4, \\ W_2 &= w_2x_1 + w_5x_2 + w_4x_3 + w_8x_4, \\ W_3 &= w_3x_1 + w_4x_2 + w_6x_3 + w_7x_4, \end{aligned}$$

and

$$W_4 = w_4x_1 + w_8x_2 + w_7x_3 + w_9x_4,$$

with  $w_i$  being the elements of the fitness matrix

$$\begin{array}{c|ccc} & AA & Aa & aa \\ \hline BB & w_1 & w_3 & w_6 \\ Bb & w_2 & w_4 & w_7 \\ \hline bb & w_5 & w_8 & w_9. \end{array}$$

The mean fitness of the population is

$$\hat{W} = x_1W_1 + x_2W_2 + x_3W_3 + x_4W_4.$$

Fig. 1 represents a fragment of the phase space of a population subjected to cyclical selection with period  $p = 2$ . We considered a system with fitness matrices in the two environmental states presented, up to multiplicative constants, as:

$$S_1 = \begin{vmatrix} 3.6160 & 1.8870 & 1.370 \\ 2.7910 & 1.7103 & 0.763 \\ 2.6455 & 1.5080 & 0.586 \end{vmatrix}$$

and

$$S_2 = \begin{vmatrix} 0.263435 & 0.529942 & 0.736377 \\ 0.351989 & 0.586295 & 1.285347 \\ 0.386399 & 0.663130 & 1.706485 \end{vmatrix}. \quad [1.2]$$

Fig. 1 displays the phase portrait of the system for  $r = 0.303$ ; the phase point was taken at the end of the environmental period.

This system has a stable limiting supercycle with the period length of about 1100 environmental periods (2200 generations) and a stable polymorphic point (i.e., a cycle of forced oscillation with the period  $p = 2$ ). It is noteworthy that the effect of supercycling on the range of variations in allele frequencies at the selected loci is nontrivial. For the considered example,  $\delta P_A$ , the difference between the maximal and minimal values of allele frequencies along the supercycle for locus  $A/a$  is 0.62 and for  $B/b$ ,  $\delta P_B$  is 0.39. The difference between  $P_A$  and  $P_B$  values within any environmental period varies only within the range (0.00, 0.14) for  $\delta P_A$  and (0.00, 0.08) for  $\delta P_B$ . For the indicated start points in Fig. 1, the described pattern of behavior could be observed for recombination values  $r \in (0.300, 0.306)$ . At  $r < 0.3$ , the limiting supercycles disappear. At  $r > 0.306$ , both limiting cycles disappear, but the polymorphic limiting point remains stable.

Supercyclical behavior could be observed under different selection regimes. Another example, with environmental period  $p = 4$ , will be described below in the discussion of a model involving recombination modifier. The ability to supercycle autooscillations will result in an increase in the range of population variation in a long-term scale. This effect may complicate interpretations of gene frequency patterns in natural populations. The complexity of mean fitness ( $\hat{W}$ ) behavior

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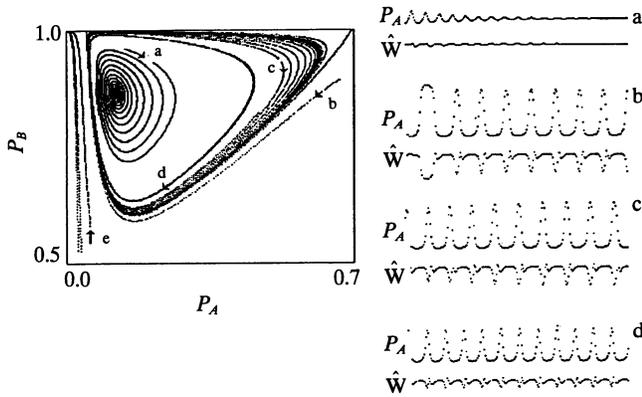


FIG. 1. Supercyclical behavior of a diploid two-locus population subjected to cyclical selection with a period  $p = 2$ . Projections of the phase space on the plane of allele frequencies ( $P_A, P_B$ ) are shown with the points of the phase trajectories representing ends of the environmental periods. The following trajectories are shown: a, converging to the stable polymorphic point (for the trajectory in the figure, the following initial point was used  $x_1 = 0.057, x_2 = 0.010, x_3 = 0.761$ , and  $x_4 = 0.172$ ); b, converging to the stable supercycle from the "outside" (we started from the initial point  $x_1 = 0.52, x_2 = 0.05, x_3 = 0.38$ , and  $x_4 = 0.05$ ); c, converging to the stable supercycle from the "inside" (we started from  $x_1 = 0.40, x_2 = 0.00, x_3 = 0.41$ , and  $x_4 = 0.19$ ); d, an unstable supercycle separating the domains of attraction of the stable point and the stable supercycle (the starting point was  $x_1 = 0.232201, x_2 = 0.002704, x_3 = 0.741072$ , and  $x_4 = 0.024021$ ); e, trajectories converging to the trivial fixed point. Here and in the following illustrations the starting points correspond to the first state of the environmental period (selection regime defined by the matrix  $S_1$ ). Graphics in the right part show temporal variation in  $P_A$  and population mean fitness changes (as geometric means over the environmental period) for trajectories a–d.

(see Fig. 1, trajectory b) along the supercycle may have ecological consequences, allowing for speculations on possible mechanisms of ecological cycles revealed in nature (7, 8). Long-term autooscillations (while damping ones) were found in our haploid two-locus models (9).

### Single-Locus Multiallelic Diploid Model

Let us consider a two-locus system with  $r = 0$ , subjected to cyclical selection with period  $p = 2$ . The evolutionary operator (Eq. 1.1) with fitness matrices

$$S_1 = \begin{vmatrix} 3.6160 & 1.8961 & 1.3700 \\ 2.8001 & 1.7103 & 0.7721 \\ 2.6455 & 1.5171 & 0.5860 \end{vmatrix}$$

and

$$S_2 = \begin{vmatrix} 0.263435 & 0.529523 & 0.736377 \\ 0.361089 & 0.586845 & 1.280797 \\ 0.386399 & 0.658580 & 1.706485 \end{vmatrix}$$

was used in our numerical runs.

Because  $r = 0$ , the haplotypes  $AB, Ab, aB$ , and  $ab$  could be interpreted as four alleles ( $h_1, h_2, h_3$ , and  $h_4$ ) of a single locus, with a special assumption that  $w(h_1h_4) = w(h_2h_3)$ .

The obtained pattern of the described system is shown in Fig. 2. Clearly, the model behaves as one locus with four alleles. The phase space contains an unstable supercycle and a polymorphic stable point, the last one residing in the subspace  $h_2 = 0$  (see Fig. 2). Thus, the supercyclical behavior is a characteristic also of the three-allelic system. The difference between Figs. 1 and 2 should be determined by opposite signs at the quadratic term of the expansion of the evolutionary operator

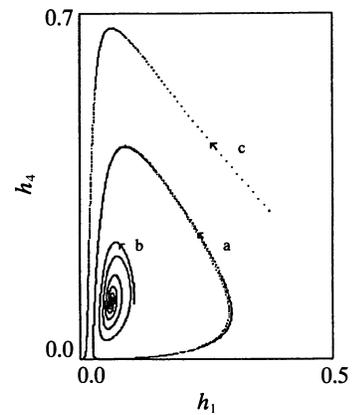


FIG. 2. Supercyclical behavior of a diploid single-locus population with four alleles subjected to cyclical selection with a period  $p = 2$ . Three types of limiting behavior can be observed. Trace a shows that starting from the initial point  $h = (h_1, h_2, h_3, h_4) = (0.232201, 0.002704, 0.741072, 0.024021)$ , the unstable supercycle will be obtained. This supercycle is a saddle-type one because it attracts, for example, the trajectory that starts at the above mentioned interior point  $h$ , but in the subspace  $h_2 = 0$ , it is a repeller for any tested point in its proximity. Trace b shows that by starting from  $h = (h_1, h_2, h_3, h_4) = (0.107, 0.020, 0.761, 0.112)$  (as an example), the trajectory will converge, by dumping superoscillations, to the stable point. On the plane  $(h_1, h_4)$ , the stable point lies inside of the unstable supercycle. Trace c shows that the initial point  $h = (h_1, h_2, h_3, h_4) = (0.386261, 0.042068, 0.284591, 0.287080)$  results in fixation of allele  $h_4$ . On the right of the figure, respective changes in the mean fitness along the trajectories are shown.

in proximity of the fixed point (10). Therefore, the ability to supercyclical oscillations in the above two-locus system with  $r = 0$  is, in a sense, derived from the one-locus system.

It is noteworthy that the existence of a limiting supercycle, even unstable, with non-monotonic behavior of the mean fitness, makes it rather improbable to generalize Fisher's Fundamental Theorem on the case of one-locus selection in a fluctuating environment.

### Two-Locus Selected System and a Recombination Modifier

The analysis of the above two-locus model showed that recombination is a crucial factor affecting the limiting behavior. Namely, only with  $r$  from some interval,  $r_0 < r < r_1$ , can stable supercycles be observed. What will happen if  $r$  is not fixed in the population; what changes would be observed, if we incorporate into the model a selectively neutral *rec* modifier (11–14)?

Computer modeling was based on the iteration of standard equations of a three-locus system (two selected loci and a *rec* modifier) (e.g., ref. 15; for the genetic scheme, see Fig. 3A), with selection coefficients depending on the environment. We considered a two-state environment with period  $p = 4 (2 + 2)$ . The following matrices were used:

$$S_1 = \begin{vmatrix} 3.6160 & 1.8870 & 1.3700 \\ 2.7910 & 1.7103 & 0.7630 \\ 2.6455 & 1.5080 & 0.5860 \end{vmatrix}$$

and

$$S_2 = \begin{vmatrix} 0.263435 & 0.531863 & 0.736377 \\ 0.353910 & 0.584145 & 1.287268 \\ 0.386399 & 0.665051 & 1.706485 \end{vmatrix}$$

With this selection regime, a decrease in  $r$  below a border  $r = r_0$  leads to tightening of the supercycle to the fixed point, while

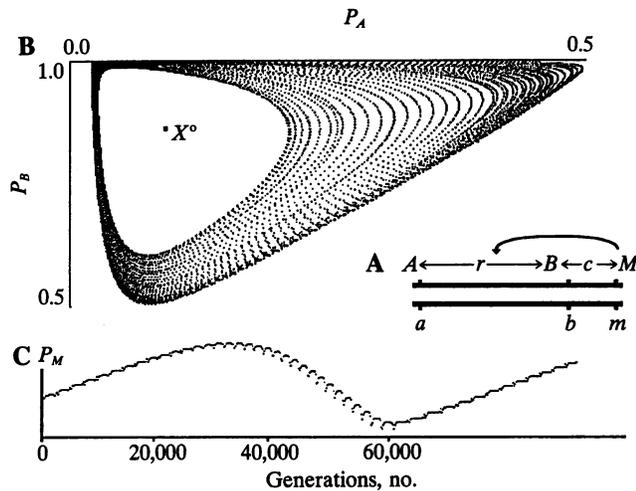


FIG. 3. Stable super supercyclical autooscillations in a model incorporating a two-locus selected system and a recombination modifier. (A) The structure of the genetic system. (B) A fragment of the phase plane ( $P_A$ ,  $P_B$ ) with the super supercycle. (C) Time dependence of the frequency of allele  $M$  for high recombination ( $R_M = 0.5$ ). Recombination values determined by the modifier were  $R_{mm} = 0$ ,  $R_{MM} = 0.5$ , and  $R_{Mm} = 0.5$  ( $R_{mm} + R_{MM} = 0.25$ ); the crossing-over rate between the modifier and selected system was  $c = 0.005$ . Let first the modifier be fixed. Starting from  $x = (x_1, x_2, x_3, x_4) = (0.40, 0.00, 0.41, 0.19)$ , we obtain for the selected system the same types of behavior as in Fig. 1, while for other recombination rates between the selected loci, namely, for  $r_0 < r < r_1$  ( $r_0 = 0.24$ ,  $r_1 = 0.33$ ), a stable supercycle could be observed. A decrease in  $r$  below  $r = r_0$  leads to tightening of the supercycle to the polymorphic fixed point  $X^0$  (i. e., forced oscillations with  $p = 4$ ). An increase in  $r$  above  $r = r_1$  results in superoscillations with an ever increasing superperiod. In the vicinity of  $X^0$ , selection favors increased recombination, provided  $c$  is not too small (e.g.,  $c > 0.001$ ). On the other hand, supercyclical autooscillations with a very long period (for  $r = r_1 = 0.33$ , our supercycle amounts to 3400 generations) will favor low recombination. Interaction of these forces leads to the appearance of a stable super supercycle (B) with corresponding oscillations in the modifier frequency (C). In the example presented, we started with the frequency of nonzero recombination allele  $P_M^0 = 0.5$ ,  $M/m$  locus being in linkage equilibrium with the selected system.

an increase in  $r$  above some  $r = r_1$  results in superoscillations with ever increasing superperiod and amplitude.

The fate of the modifier locus  $M/m$  will depend on two forces: fast environmental fluctuations (period  $p = 4$  generations) and supercyclical oscillations with a period of 2000–3000 generations. It is known that the mode of modifier dynamics could critically depend on its linkage to the selected system (14, 16, 17). We found that, in our model, for some range of linkage values between the selected system and  $M/m$ , a kind of variable “balance” of the above two forces could be achieved, leading to regular stable fluctuations in the two-locus supercycle characteristics: repetitive changes in its amplitude and period length (see Fig. 3B). While this attractor seems to be rather complex, trajectories starting from neighboring initial points do not diverge. Thus, we could refer to such a regime as a stable “super supercycle.” Obviously, the modifier fluctuates with a period equal to that of the super supercycle (Fig. 3C). It is important to note a peculiarity of the system dynamics caused by polymorphism for the *rec* locus: preservation of supercyclical mode of behavior in a much broader range of phase states.

The super supercycle moves in the same domain of the phase space, when attracting to or repelling from the fixed point ( $x^0$ ). However, some of the characteristics of this movement depend not only on the position of the system phase coordinates in the phase space but also on the direction of this movement. By an analogy with physics, this mode of the three-locus system

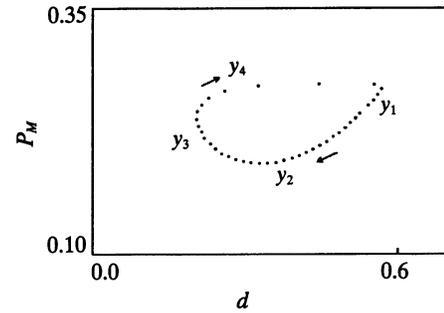


FIG. 4. Hysteresis-like behavior of the three-locus system. The graph represents a schematically proposed mechanism of the observed behavior of the system described in Fig. 3. Here  $P_M$  and  $d$  are the frequency of high recombination allele and distance of  $\max(P_A)$  on the supercycle to  $X^0$  for every super-period. Let us start from a remote, with respect to  $X^0$ , supercycle (point  $y_1$ ). Because of the long period, selection will promote evolution for decreased recombination and, thereby, for ever-increasing attraction of the trajectory to the fixed point  $X^0$  (phase  $y_1$ - $y_2$ ). With decreasing amplitude of the supercycle, the oppositely acting factor (forced oscillations with  $p = 4$ ) overcomes and recombination starts to increase (phases  $y_2$ - $y_3$  and  $y_3$ - $y_4$ ). However, in the vicinity of  $y_3$ , recombination crosses a level that corresponds to repelling of the trajectories from  $X^0$ . Then, the supercycles with increasing amplitude and periods will again prevail over the forced oscillations, resulting in reduced recombination (phase  $y_4$ - $y_1$ ).

behavior could be referred to as a “hysteresis” effect in population dynamics (Fig. 4). Linkage of the modifier locus to the selected system, a kind of an “inertia factor,” is the key component determining the very possibility of such a pattern. Moreover, without close enough linkage, polymorphism for the modifier locus would hardly be possible,  $m$  tending to fixation during the slow supercycles (around phase  $y_1$  in Fig. 4).

Discussion

Two questions are of importance with respect to the revealed mode of population behavior: (i) the volume of convergence to the limiting supercyclical trajectory and (ii) structural stability (i. e., qualitative independence of the supercyclical mode of dynamics on the system parameters).

Concerning the first question, we mention that for the example of Fig. 1, a domain in phase space could be found  $\pi = (x_2, x_4 < 0.1$  and  $x_1, x_3 > 0.2)$  so that 80% trajectories starting from  $\pi$  converge to the stable supercycle. In the model of Fig. 3, 50% of starts from  $\pi$  with  $P_M^0 = 0.5$  have resulted in convergence to the super supercycle.

Clearly, the problem of structural stability in such an unusual behavior as supercycles and super supercycles is rather complex, as in other intricate regimes (e. g., chaotic-like ones). In addition to the two (rather different) selection regimes described in the foregoing models, a set of analogous situations may be found. Namely, let selection be defined by pairs of fitness matrices  $S_1$  [with elements  $w_i^{(1)}$ ,  $i = 1 \dots 9$ ] and  $S_2$  [with elements  $w_i^{(2)}$ ,  $i = 1 \dots 9$ ]. Then, the desired supercyclical behavior will be manifested by the model provided  $w_i^{(1)}w_i^{(2)} \approx \alpha$ ,  $i = 1 \dots 9$ , where  $\alpha$  is some positive constant. A similar condition was considered in our analysis (9) of damping superoscillations caused by haploid selection. With the above condition, additional examples of supercycles and super supercycles could easily be provided. The following are two such examples: (i) Supercycle will be obtained for the period  $p = 1 + 1$ ,  $r = 0.13$ , and

$$S_1 = \begin{vmatrix} 3.51600 & 1.78700 & 1.27000 \\ 2.77100 & 1.39030 & 0.74300 \\ 2.74550 & 1.60800 & 0.68600 \end{vmatrix}$$

and

$$S_2 = \begin{vmatrix} 0.270643 & 0.559038 & 0.793572 \\ 0.354169 & 0.705522 & 1.318600 \\ 0.372689 & 0.622512 & 1.459184 \end{vmatrix}$$

starting from  $x_1 = 0.383459$ ,  $x_2 = 0.000000$ ,  $x_3 = 0.447368$ , and  $x_4 = 0.169173$  (at first environmental state). (ii) Super super-cycle will be obtained for the period  $p = 2 + 2$ , with  $R_{mm} = 0$ ,  $R_{MM} = 0.25$ , and  $R_{Mm} = 0.5$  ( $R_{mm} + R_{MM}$ ) = 0.125; crossing-over rate between the modifier and the selected system may be any value from the interval  $0.005 < c < 0.1$ , and

$$S_1 = \begin{vmatrix} 3.51600 & 1.78700 & 1.2700 \\ 2.77100 & 1.60030 & 0.7430 \\ 2.74550 & 1.60800 & 0.6860 \end{vmatrix}$$

and

$$S_2 = \begin{vmatrix} 0.270643 & 0.559038 & 0.793572 \\ 0.354169 & 0.626971 & 1.318600 \\ 0.372689 & 0.622512 & 1.459184 \end{vmatrix}$$

starting from  $x_1 = 0.383459$ ,  $x_2 = 0.000000$ ,  $x_3 = 0.447368$ , and  $x_4 = 0.169173$  (at first environmental state) with the frequency of nonzero recombination allele  $P_M^0 = 0.5$ .

Therefore, we have shown, that cyclical selection caused by short-term environmental fluctuations can result in two levels of stable superoscillations composed of hundreds and dozens of thousands of generations. These results could change our

view on the role of short-term cyclical genetic processes in natural populations. Under some selection regimes, a “properly” organized system could develop its own pattern of behavior in an evolutionary significant time scale.

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