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GAME THEORY AND POPULATION DYNAMICS IN COMPLEX GENETICAL SYSTEMS: THE ROLE OF SEX IN SHORT TERM AND IN LONG TERM EVOLUTION

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Abstract

The article maintains three major points:

(i) In sexual populations with recombination, there is qualitative difference between one process of natural selection which manifests itself in terms of changes of frequencies of genotypes already present in the population (say, short term selection) and another process which manifests itself in terms of selective gene substitutions (say, long term selection).

(ii) It is only the process of long term selection (due to gene-substitutions) and not the process of short term selection (due to change in genotype frequencies) that quite generally, leads to the individual optimization of certain evolutionarily relevant payment functions and thus, guarantees the stabilization of ESS population strategies.

(iii) These findings, being based on theoretical analysis of the well studied genetic structure of sexual reproduction, are well fitted into the main bulk of current theories about the evolution of the sexual system of reproduction in a changing environment. They can, in turn, throw some new light on the role of sex in preventing fast adaptation to short term, non persisting environmental changes and, at the same time allowing (and, as being maintained in this work, even facilitating) slow adaptation to long term, persisting environmental changes.

§1 Game Theory and the dynamics of Evolutionary Changes in Complex Sexual Systems - The Problem

An indispensable theoretical strategy in the struggle of modern biology to cope with the complexity of patterns, either behavioral, physiological or biochemical, exhibited by natural organisms, is the tendency to explain such patterns on the basis of their adaptive value to the organism exhibiting them. In the core of such tendency lays the crucial, though sometimes tacit, assumption that natural selection is bound to operate towards the optimization of certain biological traits, at least on the level of the individual (though not necessarily on the level of the population, e.g. Williams 1966). Tacitly, this assumption becames a synonym to Darwinism. Indeed, when one keeps in mind the idea of individual optimization in respect to conflicts within a population, population game theory and the concept of ESS become indispensable tools to analyze the outcome of the conflict.

Concerning, however, the applicability of population game theory to the real dynamics of evolutionary changes in sexual diploid populations, the question is, indeed, what relevant payment function, if any at all, tends to be maximized (at least locally and on the individual level) by the combined effect of the mating system (say, even the random one), Mendelian segregation, recombination (when more than one locus is involved) and the selection pressure when manifested on the level of viability, fertility, sexual success or, more generally, maybe inclusive fitness. Thus, in the simplest (though most widely studied) case of a two strategy viability population game in a one locus, random mating (infinite) population, changes in the genotype frequencies are proved to always determine either convergence of the population strategy to an ESS of the genetically feasible strategies or oscillation around it. Moreover, with some upper-bound on the intensity of selection (measured in terms of ratio between the extreme values of the payment function), convergence to the viability-ESS is the only possibility (Eshel 1982, Lessard 1984, Karlin and Lessard 1984. See also discussion in Maynard Smith 1982).

Unfortunately, these results remain true for only singular cases when more than one locus is involved. Moreover, as it has been first pointed out by Moran (1964), quite counterintuitively at first sight, in a random mating diploid population with viability determined by two loci or more, natural selection does not guarantee an increase in the average viability of the population even under the condition of a fixed environment. Since then, this apparent contradiction to the Darwin-Fisher-Wright expectation has been shown to occur in most multilocus nonadditive fitness regimes (Ewens 1969; Lewontin 1971; Karlin 1975). As a result, even in a constant environment and even when only individual viability is involved it cannot be generally true that natural selection operates to produce an optimal population strategy. It is, therefore, not surprising that in a population-game viability structure (see Maynard Smith and Price 1973), when more than one locus is responsible for the individual strategy, genetic equilibria are most unlikely to determine an ESS distribution of phenotypes even when such distribution is feasible (Lessard 1984) *this in contrast to the case of one locus.*

The situation becomes even worse if viability is replaced by any other "natural" payment function, say inclusive fitness (Hamilton 1964, 1971), expected number of grandoffspring (e.g. Fisher 1930) or even fertility. Thus, it has been shown by Hadeler and Liberman (1975) that average fertility is not generally maximized even by natural selection at one locus; and it has been shown by Cavalli Sforza and Feldman (1978) and by Uyenoyama and Feldman (1981) that even the inclusive fitness is not monotone increasing under one locus selection pressure (but it is locally maximized at a one locus fixation). None of these is, indeed maximized by the multilocus dynamics (indeed, the viability-selection counter-example is sufficient for this because it can be represented as equivalent to special cases of either fertility-selection or inclusive fitness-selection). All the same it was shown by Karlin and Lessard (1986) that selection on the sex ratio, when determined by two loci, is not likely to lead to a stable equilibria that maximize the expected number of one's grandoffspring, contrary to the prediction made by Fisher (1930) and to the result achieved by Eshel and Feldman (1982) for a one locus case.

I think that these seemingly counter-intuitive and rather disturbing findings should not be overlooked on the basis of simple minded common sense. It is true that they are deduced from an analytically complicated structure which is sometimes hard to follow by simple intuitive arguments, but so is the very process of reproduction in a complex multilocus sexual system and, indeed, one should keep in mind that it may be even harder to explain, on the basis of simple minded common sense, the very evolution of this complex structure of reproduction, say the evolution of sex itself. But we do, in fact, reproduce sexually.

During the last decade, many attempts have been made to explain the evolution of sex on the basis of exact genetic models, e.g. Maynard Smith (1971a,b, 1975, 1978), Williams and Mitton 1973), Hamilton (1980,1982), Hamilton et al. (1981), Weinshall (1986), Weinshall and Eshel (1987), Bell and Maynard Smith (1987), Bernstein et al. (1983, 1984). With the exception of the last one, all these attempts converge on the assumption of some sort of irregularity of the environment as a necessary prerequisite for the establishment of sexual reproduction in a population. Later in this work (see §5) I will try to maintain that the same structure that allows us to explain the evolution of sex in an irregular environment is most likely to explain as well the seemingly "non adaptive" failure of the multilocus system to stabilize individually optimal strategies in sexual populations due to selective change in genotype frequencies.

But maybe a more disturbing aspect of this analytically established but intuitively unwelcome result has to do with its apparent theoretical implication on the most crucial component of Darwinism, say the causal bond between natural selection and adaptation. Does it, indeed, mean that near optimality (or, as well, mutual optimality, say ESS) is not likely to be observed when complex features in sexual populations are concerned? Such theoretical prediction would indeed stand in contrast with many observations of both complex and amazingly close to optimal traits like flight-ability, eyesight or programmed nest-building, to mention a few traits which are rather found in sexual populations and, undoubtedly involve many recombining genes. Another property of these traits, however, is that they are all likely to evolve throughout a long process of "trial and error", say by successive replacements of genes rather than by change of relative frequencies within a given set of genotypes. And, as we see in the next two sections (see §2 for viability selection, §3 for other modes of selection) contrary to a widely accepted though tacit assumption, this long term process of selected gene substitution is qualitatively different from the extensively studied process of change in genotype frequencies.

We should, therefore, start by a clear distinction between the two processes, that of *short term selection* (namely due to changes in genotype frequencies) and *long term selection* (namely due to selected gene substitution). On the basis of a bulk of quite recent theoretical findings we see that, contrary to short term selection, the hitherto less studied process of long term selection does lead, in fact, to the establishment of individually optimal and mutually optimal strategies, say ESS.

Moreover, in §4 we see how evolutionarily relevant payment functions, to be optimized by the process of long-term selection in multilocus sexual populations, can be analytically deduced from the system (i.e. from the genetic structure and the selection forces operating on it) rather than assumed on pure intuitive arguments.

Finally, I try to explain the qualitative difference between the two processes of selection on the basis of the very role of sex in evolution as it appears to follow from modern quantitative theories about the evolution of sex.

§2 Selective Gene Substitution and Long Term Convergence to an ESS in a Viability Population Game

Let us start from the simplest case of pure viability selection operating on a large diploid population with random mating and no family structure and let us assume the most general two locus system of genotype determination of the individual phenotype (or strategy). More specifically, let $A_1, ..., A_n$ be the alleles present in one locus and $B_1, .., B_m$ the ones present in the other locus. Let $0 \leq r \leq \frac{1}{2}$ be the rate of recombination between the two loci. The genotypes are A_iB_k/A_jB_ℓ where $i, j = 1, 2, \ldots, n$; $k, \ell = 1, 2, \ldots, m$.

Let us assume that individuals of different genotypes are different only in their viability and let $\omega_{ijk\ell}$ be the viability of the genotype A_iB_k/A_jB_ℓ. $\omega_{jik\ell} = \omega_{ijk\ell} = \omega_{ij\ell k} = \omega_{ji\ell k} \geq 0$. Finally, let p_{ik} be the relative frequency of the chromosome A_iB_k passed to newborn offspring in the population. With random mating and Hardy Weinberg law for combination of gamates after recombination, the average viability in the population is, therefore:

$$W = \sum_{ijk\ell} P_{ik} P_{j\ell} \omega_{ijk\ell} \tag{2.1}$$

By straightforward calculation one gets the frequency of the chromosome A_iB_k after random mating, recombination and selection.

$$p'_{ik} = \frac{1}{W}\sum_{j\ell}[(1-r)p_{ik}p_{j\ell} + rp_{i\ell}p_{jk}]\omega_{ijk\ell} \tag{2.2}$$
$$i = 1,\ldots,n; k = 1,\ldots,m$$

As we know to be the general case in multilocus systems, $W = W(\underline{p})$ is not a Liapunov function of the transformation and it is possible that $W(\underline{p}') < W(\underline{p})$. Moreover, a stable equilibrium of the system may not (and quite often, does not) maximize the average viability of the population, even locally (e.g. Karlin 1975). As having been noted by Moran (1964) this means that as the genotype frequencies are changing due to random mating, recombination, Mendelian segregation and natural selection, the average viability of a population near equilibrium may monotonously drop down from one generation to the next, tending from above to a lower bound which is only materialized at the equilibrium itself.

But as it can be shown (Eshel and Feldman 1984; see also Liberman 1988 for generalization of this result to any number of loci!) the situation is different if we start from a population which is already in an internally stable equilibrium (i.e. in respect to change in the frequencies of those genotypes already in the population) and ask about successful invasion of such a population by a new, random mutant. As it turns out, one can solve this problem quite generally without resorting to any explicit information about the specific distribution of genotypes at equilibrium (an information which, as known to students of multilocus system, is rather impossible to obtain analytically in general).

Actually, employing (2.2) one only needs the equilibrium condition

$$p_{ik} = \frac{1}{W}\sum_{j\ell}[(1-r)p_{ik}p_{j\ell} + rp_{i\ell}p_{jk}]\omega_{ijk\ell} \tag{2.3}$$
$$i = 1,\ldots,n; k = 1,\ldots,m$$

Without loss of generality we may assume now that the new mutant allele is introduced into the first locus. This allele, say A_{n+1} may appear in combination with each of the alleles at the other locus, thus let $\varepsilon_k (k = 1,\ldots,m)$ be the frequency of the mutant chromosome $A_{n+1}B_k$. Let $\varepsilon = \sum_{k=1}^{m}\varepsilon_k > 0$ be a small number. Finally we take over the standard assumption that the frequencies of those chromosomes A_iB_k already presented at the original equilibrium are not changed by more than the order of ε as a result of the first invasion of the mutant. Employing (2.2) for the dynamics of the new $(n+1,m)$ allele system and ignoring terms of the order of ε^2 we get

$$\varepsilon'_k = \frac{1}{W}\sum_{j\ell}[(1-r)\varepsilon_k p_{jk} + r\varepsilon_k p_{jk}]\omega_{n+1,j,k,\ell} \tag{2.4}$$

where W is the average equilibrium viability, defined in (2.1).

Following the Perron Frobenius theorem, it can be shown that the transformation $\underline{\varepsilon} \to \underline{\varepsilon}'$ being determined by (2.4) has a unique positive leading right eigenvector $V_1, \dots, V_m$ corresponding to the (positive) leading eigenvalue $\lambda > 0$. The mutant will, indeed, be established in the population if $\lambda > 1$ (and only if $\lambda \geq 1$).

As it can be shown (Eshel & Feldman 1984, Liberman 1988), $\lambda > 0$ if and only if

$$\frac{1}{\sum_{k=1}^{m} V_k} \sum_{jk\ell} V_k P_{j\ell} \omega_{n+1,j,k,\ell} > W \tag{2.5}$$

Equivalently, let $\underline{\varepsilon}$ be in the direction of the right eigenvectors $\underline{V}$, than the mutant will become established in the population if

$$W < \frac{1}{\varepsilon} \sum_{jk\ell} \varepsilon_k p_{j\ell} \omega_{n+1,jk\ell} = W_{n+1}, \quad \text{say} . \tag{2.6}$$

But the righthand side of (2.6) is the average viability of a random mutant in the population. Moreover, the average viability of the population, with $\underline{\varepsilon}$ deviation from the equilibrium is $(1-\varepsilon)W + \varepsilon W_n$. Hence we get, as a corollary:

A new mutant, being introduced into the population will be successfully established if and only if it initially increases the average viability of the population, at least in the direction of the leading right eigenvector. (Eshel and Feldman, 1984).

But then note that the relative frequencies of the mutant chromosomes tend to the components of the (normalized) leading right eigenvector, if converging or else, even if diverging they get as close to these components as we wish before leaving the ε-vicinity of the equilibrium, provided we start with an even smaller (say, small enough) deviation. Hence one can conclude that starting from any two locus viability equilibrium, a new mutation will successfully enter the population if and only if it initially increases the average viability at least in the direction of the main eigenvector of the population. (See for comparison Taylor 1985).

Furthermore, assume now a population-game-structure of viability selection, i.e., let each individual in the population choose one of the N strategies $\alpha_1, \dots, \alpha_N$ and let the probability that an individual of genotype A_iB_k/A_jB_ℓ choose the strategy α_ν be $S_{ijk\ell}^{(\nu)}$. Indeed $S_{ijk\ell}^{(\nu)} \geq 0$ and $\sum_{\nu=1}^{N} S_{ijk\ell}^{(\nu)} = 1$ for all $i, j = 1, \dots, n; k, \ell = 1, \dots, m$. Let the relative frequency of the chromosome A_iB_k among newborn offspring be p_{ik}, as before, then the population strategy $\underline{S}$ will be

$$S_\nu = \sum_{ijk\ell} p_{ik} p_{j\ell} S_{ijk\ell} \qquad \nu = 1, \dots, N . \tag{2.7}$$

Assume now that individuals in the population meet at random and the payment function of an individual playing α_ν against an opponent playing α_μ is $m_{\nu,\mu}$, payment being measured in terms of an additive component of the viability. We get a general two locus, linear frequency dependent viability system in which the viability of the genotype A_iB_k/A_jB_ℓ is given by

$$\omega_{ijk\ell} = \omega_{ijk\ell}(\underline{p}) = \tag{2.8}$$
$$= \sum_{\nu=1}^{N}\sum_{\mu=1}^{N} S^{(\nu)}_{ijk\ell} S_\mu m_{\nu,\mu}$$

where the $S_\mu = S_\mu(\underline{p})$ are given by (2.7). Consider first the simplest case of a 2×2 population game ($N = 2$) dealt in §1, we have seen (e.g. Lessard 1984) that, concerning changes in two-locus genotype frequencies, an ESS of the population game is likely to be unstable and natural selection, combined with random mating and recombination, can render the population strategy further apart from the ESS. If, on the other hand, the population is already in a stable equilibrium, determining a population strategy close to an ESS, one can use a similar technique in order to show that a new mutation will be established in the population if and only if it initially renders the population strategy closer to the ESS, at least when the relative frequencies of the mutant-chromosomes approaches the direction of the main eigenvector. No mutation can successfully invade a population which already determines an ESS population strategy. This last result is true, moreover, for any (N strategy) population game. If the population is, then, only close to an ESS, a new mutation will, successfully invade it if it initially shifts the population strategy into a strategy-cone in the direction of the ESS. Also these results (Eshel & Feldman 1984) have recently generalized by Liberman (1988) to any number of loci.

§3 Other relevant payment functions and Evolutionary Genetic Stability (EGS)

A similar approach can lead to the demonstration of a long-term maximization of other payment functions, depending on the specific (short term) forces of selection operating on the population.

Thus, the general n-locus result for initial increase under viability selection has been also generalized by Liberman (1988) to the most general case of sex-dependent viability. In this case, the condition to initial increase in the frequency of a new mutant at any of the m involved loci is

$$\frac{1}{2}\left(\frac{W_f^*}{W_f} + \frac{W_m^*}{W_m}\right) > 1 \tag{3.1}$$

where W_f and W_m are the population-average viabilities of females and males respectively at (internal) equilibrium, W_f^* and W_m^* are the average viabilities of (heterozygote) mutant females and males where the distribution of mutant chromosomes is in the direction of the main eigenvector. In the case of a trade-off restriction $W_f = h(W_m)$ between male and female viabilities (e.g. where phenotypic features which are advantageous for one are disadvantageous for the other), one gets stability to any new mutation (at any locus), affecting W_m (and thus $W_f = h(W_m)$) if and only if the function

$$F(W_m, X) = \frac{1}{2}\left(\frac{X}{W_m} + \frac{h(x)}{h(W_m)}\right) \tag{3.2}$$

is maximized for $X = W_m$ (where it obtains the value 1).

In all other cases, natural selection will operate in favor of those mutants which (by changing $W_m^* = X$) increase the value of $F(W_m, X)$, thus long term natural selection operates for individual increase of the payment function F. ?

But it can readily be shown (Liberman et al. 1989) that F is the expected number of grand-offspring, male and females altogether, descending from an adult (heterozygote) mutant, either male or female. The result being obtained therefore follows and generalizes the argument of Fisher (1930) for the individual maximization of grandoffspring number by shifting the sex ratio in the direction of 1 : 1 (see also Eshel 1974 for detail). [illegible]

Thus, it can be shown that in the most general, one locus autosomal system of sex determination, a new mutation without pleiotropic effect (i.e. mutation that affects only the sex ratio) will successfully be established in the population if and only if it initially render the population sex ratio closer to 1 : 1 (Eshel & Feldman 1981). In this case, it was further proved by Karlin & Lessard (1983, 1984) that the sex ratio corresponding to the newly established equilibrium will be closer to it than the old one. Yet they have maintained (Karlin & Lessard, 1986, see also Feldman and Otto 1989) that in a two locus system of sex determination, changes in genotype frequencies are not likely to lead to an even sex ratio, even when feasible. Instead, any sex ratio can be stably maintained, depending on the parameters of the model. [illegible]

As in the case of viability selection, however, a different result is obtained if we ask about the long term process of evolution, namely selective allele substitution. As it can be shown for the most general two multilocus autosomal system of sex determination a new mutation will be established in the population when introduced into an internally stable equilibrium (i.e. a genotype-frequency equilibrium) if and only if it initially renders the sex ratio closer to 1 : 1, at least in the direction of the main eigenvector. As being shown by Liberman et al. (1989), this result readily follows from the general sex-dependent viability model (Liberman 1988) by just formulating the model of m-locus sex determination and then formally interpreting the parameters of individual sex determination as allele mut'n at one locus

parameters of sex-dependent viability selection with the especial restriction $\omega_f = h(\omega_m) = 1 - \omega_m$. (For first observation of the general analytic equivalence of the two models, see Karlin and Lessard 1986). Moreover, in the same way it is shown that even with pleiotropic effects of sex determination, although the sex ratio of 1 : 1 is not necessarily obtained, the Fisher's criterion of grandoffspring maximization still holds for initial increase at any locus.

Following the terminology of Hamilton (1967), one can say that the even sex ratio (namely the ESS of the population game with individual maximization of grandoffspring number) and (as demonstrated in the previous section) the ESS of a viability population game are *unbeatable* population strategies, namely: If adopted by the almost entire population, this population must be stable against any new non-pleiotropic mutation, affecting the individual behavior in respect to this strategy (see also Maynard Smith and Price, 1973). Yet, in both these cases we can prove more. It is therefore worthwhile to introduce a somehow stronger concept of long term stability (Eshel and Feldman, 1981).

not
at 2 loci
one

Definition. A strategy α has the property of *Evolutionary Genetic Stability* (E.G.S.) within the genetic structure G if

(i) Any genetic equilibrium in G which determines the population strategy α is stable against any mutation that changes the population strategy (i.e: α is an unbeatable strategy in G)

(ii) Any genetic equilibrium in G which determines a population strategy $\beta \neq \alpha$, where β is close to α, is stable in face of mutation that initially render the population strategy closer to α. It is stable in face of mutation that initially renders the population strategy further apparent from α.

While the concept of dynamic stability is relevant to short term evolution (i.e. change in genotype frequencies due to a direct selection pressure) the concept of Evolutionary Genetic Stability is relevant to long term evolution (i.e. selective gene-substitution).

We see that an ESS of a viability population game has the property of Evolutionary Genetic Stability in a one locus as well as in a multilocus diploid system with random mating. This may justify the game-theory approach to viability selection, when long-term evolution is concerned. In the same way, the even sex ratio of 1 : 1 (which is the ESS for the payment function of the number of grandoffspring) has the property of EGS for a one locus as well as for the two locus autosomal system of sex determination (but it does not have the EGS property in respect to systems which involve sex linked modifiers, e.g., Hamilton 1967, Eshel & Feldman 1982b, Eshel 1984). In the same way one can show that the Mendelian (even) rate of segregation is EGS in respect to a non sex-

NO!

linked modifier of meiotic drive (Eshel 1985) but not in respect of sex-linked modifiers (Liberman 1975).

Finally, following certain assumptions about environmental fluctuations which lead to the evolution of sexual reproduction (Weinshall 1986) one can ask about the exact conditions for the establishment of a new mutation in a modifier locus that regulates the rate of (maybe partial) sexual reproduction. In this case, an EGS rate of sexual reproduction is shown to exist and can be calculated, depending on the parameter, of the process. We will return to this last example in §5.

In all these examples, a mutually "optimal" (EGS) strategy is selected in the population only throughout the long process of "trial and error" due to selective gene substitutions.

§4 Is it Possible to Infer a (Long Term) Game Structure From the (Short Term) Population Dynamics?

A serious difficulty, concerning the application of classic population game theory to biological conflicts of complicated social structure concerns the necessary assumption about the specific payment function which is supposed to be individually optimized by natural selection in that specific situation. In the previous sections we have attempted to justify the assumption of individual optimization of specific, rather simple payment functions in complex (multilocus) genetic structures, when long term selection due to gene-substitution is concerned. In some cases of biological interest, however, it is very hard to choose a "natural" candidate for such a justification since the very nature of a "descent" candidate as the inclusive fitness is rather controversial. One example is the case of workers'-queen conflict on the nest-sex-ratio in a social haplodiploid (hymenoptera) population. Another is the parents'-offspring conflict over the sex ratio in a diploid population, when the cost of rearing a male offspring is different from the cost of rearing a female one. In such case, it is possible to objectively infer the relevant payment function (if there is one) which is individually natural selection from the local dynamics of the population, rather than to speculate about it on the basis of intuitive, maybe plausible arguments.

We concentrate on the first example (the other one is now under study). As it has been suggested by Trivers and Hare (1976), the fact that (in the case of a single insemination) a mother in a haplodiploid population is equally related to her male and to her female offspring while a daughter (including a worker) in such a population is only half related to her male brother as to her female sister leads to a conflict between the mother-queen and her worker-daughters about the sex ratio among reproductive offspring of the nest. Basing their argument on the assumption of maximization of the expected number of identical-by-descent-genes, passed to the third generation, Trivers and Hare have concluded that while the queen's preferred sex ratio is 1 : 1, the workers preferred ration is 1 : 3. The expected number of identical by descent genes passed to the third generation was regarded by Trivers and Hare as the inclusion fitness.

Assuming, further, that workers-queen disagreement on the sex ratio can reduce the entire reproductive success of the next, a game-structure of the conflict naturally emerges. This is the case, for example, if a worker eats some male eggs (e.g. Trivers and Hare) or if they manipulate the proportion of differently treated reproductive and non-reproductive (worker) females (e.g. Bulmer and Taylor 1981, Bulmer 1981); or else, if the queen, in turn, lays, unfertiled eggs in a cell, allocated by workers to a fertiled egg (e.g. Matessi and Eshel 1989). A crucial question, however, concerns the relevant payment function, to be maximized by workers and queen. More specifically, since male offsprings carry half as much genes as female offspring and since (unlike in a diploid population) not all individuals, born in the population have both mother and father (males have only father), it is not clear what the "reproductive value" is (in terms of genes, passed to future generations) of a male, relative to that of a female. This has been proved, furthermore, (Oster et al 1977) to depend on the sex-ratio at a given time. Hence, so is the "value", for future generation of a gene, carried by a male or by a female offspring.

In order to avoid these difficulties, however, one can employ an exact two locus model (Matessi and Eshel 1989) - one locus affecting the queen's behaviour, another affecting workers' behaviour with any positive rate of recombination between them. Starting from a fixation -equilibrium, a mutation can appear in either the first locus, the second one or in both. It can appear in a male or in a female individual, hence one should analyse a 6-dimensional model of change in genotype-frequencies. However, as long as the rate of recombination is not too small (i.e., being higher than the maximal effect of a single mutation), a spectral analysis of the matrix of linear approximation for rare mutation of the 6-dimensional dynamics lead to two (out of six) candidates for leading eigenvalues and the condition for stability (in face of the specific pair of mutation) reduces into two separate conditions, namely that each of the two candidates for a leading eigenvalue will be smaller than one in absolute value.

More specifically, denote by $\varphi(x,y)$ the total success of a nest in which the queen's strategy is x and the (average) worker's strategy is y. Denote by $F(x,y)$ the frequency of females among reproductive of such a nest. Let α and β be the common strategy of queens and workers in the population respectively and let α and β be the relevant strategies of mutant queen being heterozygote (at the A locus) and a worker (being heterozygote at the B locus) respectively. Then, by the laborious work of solving for the linear approximation of the six dimensional transformation of genotype frequencies, one can straightforwardly calculate the two candidates for the leading eigenvalues, as:

$$\lambda_1 = \frac{1}{2}\left\{\frac{\varphi(\alpha',\beta)F(\alpha',\beta)}{2\varphi(\alpha,\beta)F(\alpha,\beta)} + \frac{1}{2}\sqrt{\left(\frac{\varphi(\alpha',\beta)F(\alpha',\beta)}{2\varphi(\alpha,\beta)F(\alpha,\beta)}\right)^2 + 2\frac{\varphi(\alpha',\beta)[1-F(\alpha',\beta)]}{\varphi(\alpha,\beta)[1-F(\alpha,\beta)]}}\right\} \tag{4.1}$$

and

$$\lambda_2 = \frac{1}{2}\left\{\frac{\varphi(\alpha,\frac{\beta+\beta'}{2})F(\alpha,\frac{\beta+\beta'}{2})}{2\varphi(\alpha,\beta)F(\alpha,\beta)} + \right.$$

$$\left. + \sqrt{\left(\frac{\varphi(\alpha,\frac{\beta+\beta'}{2})F(\alpha,\frac{\beta+\beta'}{2})}{2\varphi(\alpha,\beta)F(\alpha,\beta)}\right)^2 + 2\frac{\varphi(\alpha',\beta)[1-F(\alpha',\beta)]}{\varphi(\alpha,\beta)[1-F(\alpha,\beta)]}}\right\} \tag{4.2}$$

(Note that the rate of recombination $r > 0$ disappears from the terms (4.1) and (4.2). It does affect, however, two of the other four eigenvalues). Indeed a population being fixed on the pair of strategies (α,β) will be stable against a specific pair of mutation, determining (as heterozygotes) queen's and workers strategies α' and β' respectively if $\lambda_1 < 1$ and $\lambda_2 < 1$ (only if $\lambda_1 \leq 1$) and $\lambda \leq 1$) . By straightforward calculation one can show that this is equivalent to:

$$\frac{\varphi(\alpha',\beta)}{2\varphi(\alpha,\beta)}\left\{\frac{F(\alpha',\beta)}{F(\alpha,\beta)} + \frac{1-F(\alpha',\beta)}{1-F(\alpha,\beta)}\right\} = \tag{4.3}$$
$$\overset{(\text{say})}{=} H(\alpha,\beta;\alpha') < 1$$

and

$$\frac{\varphi(\alpha,\frac{\beta+\beta'}{2})F(\alpha_1\frac{\beta+\beta'}{2})}{2\alpha(\alpha,\beta)F(\alpha,\beta)} + \frac{\varphi(\alpha,\beta')\varphi(\alpha,\frac{\beta+\beta'}{2})F(\alpha,\beta')\left[1-F(\alpha,\frac{\beta+\beta'}{2})\right]}{2[\varphi(\alpha,\beta)]^2F(\alpha,\beta)[1-F(\alpha,\beta)]} = \tag{4.4}$$
$$\overset{(\text{say})}{=} G(\alpha,\beta;\beta') < 1$$

Thus a population fixed on a pair of strategies (α,β) will be stable against any new mutation at either locus if both the inequalities (4.3) and (4.4) will hold for any $\alpha' \neq \alpha$ and $\beta' \neq \beta$. But by inserting $\alpha' = \alpha$ and $\beta' = \beta$, these inequalities indeed turn into equalities (Say $H(\alpha,\beta;\alpha) = G(\alpha,\beta;\beta) = 1$)) Hence, a necessary and sufficient condition for (α,β) being an *unbeatable*pair of strategies (i.e. being stable against any new mutation) is that $H(\alpha,\beta;\beta\alpha')$ will obtain its maximum at $\alpha = \alpha'$ and $G(\alpha,\beta;\beta')$ will obtain its maximum at $\beta = \beta'$. But by stating this condition, however, we formally define an asymmetric population game with $H(\alpha,\beta;\alpha')$ and $G(\alpha,\beta;\beta')$ being the payment functions of the first player, when choosing the strategy α' and the second one when choosing β' respectively, in a population playing (α,β). (See Maynard Smith and Parker, 1974; Selten 1981, 1983).

Remain to be considered are indeed the payment functions H and G which emerged from the analysis of the two locus stability. In $H(\alpha'\beta;\alpha')$ (as being defined in (4.3)) one can easily recognize the inclusive fitness of the mother, as interpreted by Triverse and Hare, namely the expected number of her own genes passed to all grandoffspring, males and females altogether. Indeed, $\frac{\varphi(\alpha'\beta)}{\varphi(\alpha,\beta)}$ is the expected number of all the reproducing offspring (relative to the population average), $\frac{1}{2}\frac{1}{F(\alpha,\beta)}$ and $\frac{1}{2}\frac{1}{1-F(\alpha,\beta)}$ are the (relative) expected numbers of her genes, passed to the third generation by a female and by a male offspring respectively, thus $\frac{1}{2}\left(\frac{F(\alpha',\beta)}{F(\alpha,\beta)}+\frac{1-F(\alpha',\beta)}{1-F(\alpha,\beta)}\right)$ is the relative expected number of mother's random reproductive offspring of her and therefore $H(\alpha_\beta;\alpha')$ is the expected number of her genes passed to (either male or female) grandoffsprings by either male of female offspring.

Yet, the inclusive fitness of a mixed-nest worker, as interpreted by Trivers and Hare, namely the number of genes, identical by descent to hers, passed to the next generation by either male or female reproduction sibs is, indeed (by the same argument)

$$(4.5) \qquad \widehat{G}(\alpha,\beta',\beta') = \frac{\varphi(\alpha,\frac{\beta+\beta'}{2})}{\varphi(\alpha,\beta})\left[\frac{3F(\alpha,\frac{\beta+\beta'}{2}}{F(\alpha,\beta)}+\frac{1-F(\alpha,\frac{\beta+\beta'}{2})}{1-F(\alpha,\beta)}\right]$$

a payment function which looks quite different from the workers' payment function $G(\alpha,\beta,\beta')$ emerging from the analysis and determined in (4.4). Note, however, that without the additional effect on the nest productivity assumed here, say with full power to the workers, as guessed by Trivers and Hare both G and $\widehat{G}$ are maximized for the sex ratio $M : F = 1 : 3$ as predicted by Trivers and Hare and further argued by Oster et al. Moreover, under quite plausible assumptions, $\widehat{G}(\alpha,\beta;\beta')$ though looks quite differently from $G(\alpha,\beta;\beta')$, leads to the same ESS when combined with an opponent payment function $H(\alpha,\beta;\alpha')$ (Matessi & Eshel (1989). In fact, it can algo be interpreted as a sort of workers' inclusion fitness, namely the number of her identical-by-descent genes passed by reproductive sisters to reproductive female offspring plus the number of such genes passed to female grandoffspring through male siblings (Matessi and Eshel 1989). Maybe more important is the fact that for mutation of small effect, the expression $\widehat{G}$ can be recognized as the inclusive fitness, calculated with the regression coefficients of relatedness, as being suggested by Uyenoyama and Bengtsson (1981, 1982). Somehow a different result is achieved when mutation can occur at very tightly linked loci. In that case, the ESS condition for the population game $(\widehat{H},\widehat{G})$ remains necessary but not sufficient for (α,β) to be an unbeatable pair of strategies.

The main point of this section is that even when the feature of the unbeatable pair of strategies (α, β) can and, for better conceptual understanding, be interpreted in terms of an ESS of a population game with plausible payment functions, there is an objective way, emerging from the analysis of the exact model, to determine these payment functions.

§5 The Role of Sex in a Short and in Long Term Evolution

In this section, I will try to establish the hypothesis that maintaining a qualitative difference between short term and long term response of a population to selection pressure is the main rôle of sexual reproduction and that this difference is manifested in all sorts of hindering effects concerning a short term response (i.e. through changes in genotype frequencies) to a short term non-persisting selection pressure, but not concerning, sometimes even facilitating, long term response (i.e. through selective gene substitution), to a persistent selection pressure.

Speaking about the role of sex in evolution one is generally concerned with one of the following two questions:

(i) How does sexual reproduction affect natural selection?

(ii) How does natural selection, operating on the level of the individual, enables the evolution of sex.

Although participants of this workshop are interested mainly in the first question, I find it hard and, sometimes misleading to deal with one of these two questions separately while ignoring the other one.

One effect of sex which was not fully comprehended till the appearance of Williams book, "Sex and Evolution" (1975; See also Eshel & Feldman 1970; Eshel 1971, 1972) is its tendency to show down and even counterbalance natural selection (or, more specifically, what we refer here as to short term selection). This is true even at the first level of one locus, re-coupling of alleles, without recombination.

In order to understand this, let us consider a one-locus polymorphism with any number of alleles. Except for the trivial case of non-selection, we know that in such polymorphic population, there must be genotypes which are more viable then the average and other which are less so (e.g. in a two allele polymorphism, the necessarily more viable heterozygotes coexist with the less viable homogygotes). Let p_i be the frequency of the allele A_i among adults, $(i = 1, 2, \ldots, n)$. We know that the proportion of the genotype A_iA_j among newborn offspring is $P_{ij} = 2p_j$ if $i \neq j$ and $P_{ij} = P_i^2$ if $i = j$. Now, if this viability of A_iA_j is $\omega_{ij} (i, j = 1, \ldots, n)$ and if the average viability in the population is $W = \sum_{ij} \omega_{ij} p_i p_j$, then the proportion of $A_i A_j$ among adults (after selection) will be, indeed $\tilde{p}_{ij} = 2\omega_{ij} p_i p_j / W$ if $i \neq j$ and $\tilde{p}_{ii} = \omega_{ii} p_i^2 / w$ if $i = j$. This obviously means that $\tilde{p}_{ij} > p_{ij}$ if $\omega_{ij} > W$ and vice versa if $w_{ij} < W$. But then, random mating with re-coupling of alleles will render the proportion of $A_i A_j$ back to p_{ij}.

In other words: *re-coupling of gametes due to Hardy-Weinberg law will always increase the proportion of those combinations which are less fit then the average and decrease the proportion of those which are more fit than the average.*

With somehow more difficulties, this result can be shown to be valid for any distribution of alleles, not necessarily at equilibrium. The non-trivial part of Fisher-Kingman's fundamental law of natural selection (Fisher 1930, Kingman 1951) can therefore be stated as following:

In a one-locus random mating diploid population under viability selection, the effect of sexual reproduction, which (except in fixation) is always to decrease the average fitness of the population, is never sufficient to overbalance the effect of selection, which is always to increase the average fitness. They are perfectly balanced only at equilibrium.

A natural question is, indeed, why not to reproduce asexually, thereby to increase the average viability of the offspring? This question becomes more serious if one takes into consideration the cost of sex. First, the two-forld cost of meiosis (e.g. Maynard Smith 1971, 1978, Williams 1975) then the cost of courtship, sexual attraction and the chance of not finding a mate. Indeed, what remains to be considered is the effect of recombination which, for long time has been assumed to enhance the rate of evolution by ever providing new combinations as a material for natural selection (Fisher 1930; Muller 1932, 1958; Crow and Kimura 1965, 1969). A missing link in this argument is that, indeed, recombination may not only create successful combinations of, maybe not that successful single-locus mutation, it can as well break down such successful combinations. And, unfortunately, it can be shown (Eshel & Feldman 1970. See also Williams 1975, Levin 1988) that the rate by which recombination destroys successful combinations of alleles is faster than the rate by which it builds them up. It is often claimed, though, that this phenomenon is true for infinite but not for finite populations (e.g. Crow 1988 and references there) but this is not quite so. The truth is that the argument, though first being proved for infinite populations, holds for finite population as well. However, the first appearance of a successful combination of alleles (in fact of *any combination of alleles*) in finite population, is indeed faster if recombination creates (and destroys) new combination in any generation. But then, it seems to me that a single 'first appearance' of any combination of alleles is of no much evolutionary importance if this combination, successful as it may be, is soon to be destroyed by recombination. Thus it appears that at least qualitatively, recombination has the same hindering effect on natural selection as re-coupling of gametes. More careful quantitative study shows, moreover, that unlike the one locus-effect of re-coupling of alleles alone, its combined effect with recombination (the only combination which produces the real effect of sex) may be strong enough as to overbalance the effect of natural selection, not only slow it, thus leading, as we have already seen, to the violation of Fisher's fundamental low of natural selection. As being concluded by Bernstein et al. (1985 quoted also by Crow 1988): "The traditional view of the consequence of sex for evolution is that sex speeds up adaptation by promoting the spread of favorable mutants and elimination of deleriorating mutation. However, we argue herer that the opposite is true; that sex acts as a constraint on adaption." Or, as stated by Williams (1988): "Levin's discussion (see Levin 1988) of fitness reduction by recombination in bacteria says, in effect, that Eshel and Feldman's unwelcome conclusion has wide applicability".

It is therefore not that surprising that even without the appalling 1 : 2 cost of meiosis, natural selection when operating in a fixed environment leads to the reduction of either outbreeding (Karlin 1968-a, 1968-b or recombination Fisher 1930, Feldman 1972, Feldman et al 1980, Feldman and Liberman 1986, Liberman and Feldman 1986).

The situation is different, however, if short term environmental uncertainty is the main source of mortality in the population. With various plausible assumptions about the mode of the environmental change one can readily show that a too fast adaptation of an asexual population to a non-persistent environmental change can easily drive such a population into a total extinction. More important to the theory of evolution is the attempt to explain the evolution of sex on the basis of quantitative models, demonstrating an increase in the frequency of sexually reproducing (or more sexually reproducing) individuals within a mixed partly sexual population exposed to selection pressure of a short term environmental uncertainty. Such uncertainties may be of either spatial character (Williams and Mitton 1973, Cohen, unpublished) or of a temporal one (Maynard Smith 1971, 1975, 1978 Bell and Maynard Smith 1987, see also Sturtevant and Mather 1938). As it appears, the most plausible candidate for a source of permanent environmental changes leading to the evolution of sexual reproduction is the interminable host parasite struggle and coevolution (Levin 1975, Glesner and Tilman 1978. Jeanike 1978, Hamilton 1980,1982,1986; Hamilton et al 1981, Brenerman 1980,1985; Bell 1982; Toby 1982; Rice 1983, Weinshal 1986; Eshel and Weinshall 1988, Weinshall and Eshel 1988, Seger and Hamilton 1988). On the basis of both empirical observation and theoretical findings (e.g. Selten 1980,1983; Eshel and Akin 1983) it appears that such host parasite coevolution is most likely to result in some sort of a permanent cyclings. These may occur simultaneously but not necessarily sinchronizingly, at the level of different loci of the same host, concerning different parasites (Eshel and Hamilton 1984). The effect of such a host-parasite cycling may not be dramatic or even conspicuous from the point of view of long term, fossil-recorded evolution nor it may have any substantial effect on the morphology or behaviour of individuals in the host population. Yet it may impose a high enough toll on the generation-to-next survival of the host population as to ensure the extinction of non-sexual clones.

For example, in the simplest to explain model, suggested by Weinshall (1986) it is shown that if the population is repeatedly infested by a cycle of parasite-types (at least 3 parasite types for a diploid population) and if, for any parasite type α_i there is a single allele A_i which makes its carrier immuned to, any non-sexual close will be wiped out within one cyle of the parasite. This is so because after an attack by α_1, only the genotypes A_1A_1, A_1A_2 and A_1A_3 will survive. Of those, only A_1A_2 is immuned to α_2 and will, thus, survive its attack. Thus no genotype carrying A_3 will remain to successfully face the attack of α_3. As for sexual individuals in the same population, it can be shown that not only some of them will survive any parasite attack but, with some further (and rather plausible) assumption, the toll of death imposed by the parasite on the sexual subpopulation will not be intolerable (say, less than 50% each generation).

The reader is, indeed referred to all other models mentioned above (including some criticism of Weinshall's model in Williams 1988) yet in all of them the main role of sex (i.e. re-coupling of alleles in Weinshall's model as well as in Cohen's; mainly recombination in all other models) is just to prevent fast response to strong, short-term selection forces which are likely to change their direction and, thus, endanger the too fastly adapted non-sexual part of the population.

It should be mentioned though, that at the present stage no single theory about the evolution of sex is well-established on a quantitative level as not to leave open questions, some of them quite crucial (see, for example, Crow 1988; Williams 1988) and, indeed, some alternative explanations cannot yet be precluded. One is the old theory of sex as a short term means to "cover" deleterious mutation (Muller 1932; see also Feldman and Balkau 1972; Feldman et al 1980). Another, rather new alternative approach concerns the role of recombination in repairing DNA sequences (Bernstein 1983; Bernstein et al 1984, 1985; see also Gould and Lewontin 1979). The reader is also referred to an interesting attempt of Ettinger (1986) to explain the evolution of meiosis on the basis of its possible role in purging parasitic DNA and to an interesting speculation by Heuxtra (this volume).

I do maintain, however, that the well established, though long unwelcome finding that sexual reproduction, via all its aspects, slows down short-term selection (i.e. due to changes in genotype frequencies) and keeps genetic variance on the expense of optimization, stands quite in agreement with the basic prediction of the main bulk of theories, attempting to explain the evolution of sex on the basis of individual selection in a changing environment. From the viewpoint of this bulk of theories, the seemingly non-adaptive feature of the multilocus sexual reproduction is, indeed, adaptive in the sense of insurance against unpredictable, short term selection forces. As it has been suggested by Thompson (1976, see also Eshel 1971, 1972), the main role of sex is to slow rather than to accelerate the evolutionary response to a changing environment, and thus to act as a reign to prevent the population from chasing after transitory environmental changes. This suggestion is criticized by Crow (1988) on the basis of historical records which appear to show that a sexual species changes more slowly in evolutionary time. This argument can, indeed, turn upside down by stating the counter hypothesis that those species which were less exposed to fast environmental changes (and, therefore, changed more slowly) remained asexual. Yet, as I have tried to maintain in this work, the effect of sexual reproduction to slow down evolutionary changes, has to do only with short term aspects of natural selection. Those aspects concerning cycling changes in genotype frequencies may be crucial in coping with short term environmental changes as parasite-pressure but, as I have tried to maintain in the previous sections, they are most unlikely to leave their prints in fossil records. On the other hand, sexual reproduction may not virtually affect the slower, long term process of adaptation due to selective gene substitutions. Moreover, allowing for the short term "insurance" effect of sex, it might well be that sexual reproduction enables a higher rate of mutations and, maybe other patterns of structural flexibility, facilitating long-term evolution (for a special continuous type model predicting this possibility see Eshel 1971, 1972).

§6 Summary

We conclude that contrary to the long time widely accepted assumption of population biologists, the well studied process of changes in frequencies within a given set of genotypes, may not well represent the appropriate dynamics which is responsible for the long term evolution of either morphological or behavioural patterns in natural populations and it does not lead to the mutually optimizing structure of a population game with any payment function, except for oversimplifying singular (though easy to analyse) situations.

It is the long term process of selective gene-substitution that is likely to be responsible for the long term, fossil recorded morphological change of populations as well as to the establishment of the genetical basis for behavioral changes. This process is qualitatively different from the short term process of changes in genotype frequencies. Unlike the latter, it is likely to lead to individual optimization and, in the case of frequency dependent selection, to the convergence to ESS solutions of the population game.

As we see, these theoretical findings stands in agreement with the role of sex according to the bulk of present theories about the evolution of sexual reproductions due to selection pressure in a permanently changing environment.

Discussion.

Dan Cohen: Could you explain to us what you mean by long term and short term evolution? I mean, in terms of standatd time measure, say thousands of years or millions of years?

Eshel: I am afraid I cannot. In fact we have no good theoretical measure for the rate of evolution, especially when it involves selective gene-substitution. And in fact, we have no empirical estimation on the rate and effect-distribution of beneficial mutation. The distinction I have suggested is just qualitative. I have tried to show that there must be a qualitative difference between the short-term, well studied process of change in genotype frequencies and the long term process of selective allele-substitution. I have maintained that it is the only long-term process in which the concept of ESS and local optimization can be defended. And I have tried to show that this difference should not be that surprising as it was considered in the sixties, when counterexamples to Fisher's fundamental laws have begun to be established. They are well in agreement with the present main stream of theories about the evolution of sex and its role in natural selection.

Cohen: I still have the feeling that natural population can adapt themselves to a new environmental situation in such a short time that cannot possibly be regarded as a long-term process. Take for example the fast adaptation of insects to insecticides.

Eshel: This has admittedly happenned in quite a short time in terms of years but the process was, most likely, based on selection of new mutation occurring at one or few loci, rather than on a change in genotype frequencies. Indeed, insect populations is large enough and the length of their generation are short enough as to make long-term evolution (in the qualitative sense suggested above) quite observable to the human eye.

Cohen: This may be true but we can observe many other examples in which a natural population has overgone a very fast adaptation to human-induced environmental changes. And at least some of these examples were most likely expressing fast change in genotype frequencies. Maybe the most well known is that of the color-adaptation of the moth Biston Bettulia and related species to a black background at the time of the industrial revolution and back to white when coal was widely replaced by oil and laws for the preservation of the environment were applied.

Eshel: To quote Dick Lewontin, the fact that within more than fifty years, this example and virtually only this one, is found in any textbook of evolution, may put it as an exception that proves the rule. The fact is that lack of melanin is, often, governed by one gene and, can thus, be directly selected in agreement with the fundamental law of natural selection. still, even in this example, people tend to miss two non trivial points: first is the relative inefficiency of natural selection, even when operating on one locus in sexual, Mendelian populations. Second is the importance of this 'inefficiency' for the chance of offspring survival. Indeed, if these moths were reproducing asexually, the white variant would disappear completely and its recuperation would have to wait much longer for new mutation to occur. But my main point is that in the case of more complicated features (and concerning animal conflict, we generally deal with such features) natural selection is likely to become even less efficient in the short run, thus not even 'inefficiently' leading to optimization.

Weising: But do we really have a good general theory about natural selection in the most general multilocus system? I mean, maybe, an asymptotic one concerning very large numbers of loci.

Eshel: At this point, I am afraid not.

Weising: In this case maybe we cannot preclude the possibility that, with the increase of the number of loci, Fisher's fundamental law, tends again to become a good approximation as it is assumed in models of quantitative inheritance.

Eshel: This is a working assumption, all right, which is backed only by one's willingness to cope with the unwelcome finding about the hindering effect of sex; and it is tacitly based on the postulate of negligible epistasis. In many of the examples we are involved in, epistasis is an essential component of the non-genetic model and, thus, cannot be ignored. But still, on a hard analytical basis, I cannot preclude this possibility, in some cases.

Heuxtra: In this case one still may not need the assumption of environmental fluctuations, because sexual systems should behave very much like asexual ones.

Eshel: Except for the 1:2 cost of meiosis. In fact, I find it hard to believe that the sexual system has evolved to behave 'descently' like the asexual one, except for its being half as efficient.

Heuxtra: There is a point, indeed. Unless there is another explanation.

Eshel: That is true.

Cohen: Still, I am not sure of how really exceptional is the example of the Biston Bettulia. In fact, there is the overwhelming evidence of semi-artificial selection to which newly domesticated populations have reacted in a very rapid behavioral and morphological change.

Eshel: Indeed, there is no question about population changes as a result of selection pressure. The question is not even of adaptation but of optimization, which is absolutely different.

Weissing: It is true, though, that a breakthrough in artificial selection has occurred only when people start to combine it with inbreeding, thus to remove, in fact, the effect of sex.

Eshel: This is a very interesting remark. I never thought about it in this connotation but indeed it stands in agreement with the main thesis that short term selection is only likely to lead to an optimal peak (in respect to the selection forces) when the effects of sex are removed. Thank you.

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