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THEORETICAL PAPERS AND REVIEWS

The Uncertainty of "Fitness": What Prevents Understanding of the Role of Genetic Exchange

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Abstract—The evolutionary development of highly organized species is attained through an increase in average survival of individuals, whereas the evolution of primitive species involves only an increase in fecundity (Zavadsky, 1968). However, in population genetics, survival (or ecological resistance) and fecundity are regarded as components of a single character, fitness. Employment of the notion of fitness, which lacks a strict definition, hinders understanding of the mechanism of progressive evolution as the process that enhances ecological resistance of organisms. The notion of fitness also hinders understanding the role of genetic exchange, since the primary advantage of genetic recombination and sexual reproduction apparently is producing of progeny with high ecological resistance rather than with high genetic diversity as such. Thus, the regular genetic exchange ensures restoration of the level of ecological resistance characteristic for the species, and on the macroevolutionary scale leads to the formation of new genomes and new species with high ecological resistance.

INTRODUCTION

The most complicated issue of the modern population genetics is understanding the role of genetic recombination and the significance of sexual reproduction. In 1971, Maynard Smith was the first to unequivocally raise this question in his article entitled "What Use Is Sex?"[1]. A series of ensuing publications by different authors, in which they tried to find answers to this question, did not yield a single, generally accepted answer. Among these publications, the monographs by Williams (1975) [2], Maynard Smith (1978) [3], and Bell (1982) [4] historically have gained most recognition. Above all, their authors emphasized the paradoxical nature of sex, lying in the difficulty of finding advantages of sexual reproduction that would be comparable to the cost of maintaining sexual differentiation in populations.

Maynard Smith has most graphically demonstrated this paradox by comparing sexual reproduction and parthenogenesis in *Daphnia* [1]. These organisms are characterized by parthenogenetic reproduction, which does not require males. Owing to that fact, this mode of reproduction provides a twofold gain in fitness, measured by the rate of increase in population size. Paradoxically, this great advantage of parthenogenesis still does not result in complete elimination of sexual reproduction, though in nature the occurring fixation of advantageous mutations results in a far lower increment of fitness.

In his monograph, Bell [4] lists the most popular genetic models, designed to explain advantages of sexual reproduction, including the Fisher–Muller theory [5, 6], which is usually considered first. According to these concepts, genetic exchange promotes combining advantageous mutations that arise in different individuals of the population, which accelerates the evolutionary process. Bell named the Fisher–Muller theory "the Vicar of Bray" after a historical character that repeatedly changed his religion according to the religion of a new king. By this term, Bell probably implied that sexual process generates diversity for adaptation to ever changing environmental conditions. An important supplement to the Fisher–Muller theory was the explanation of the role of sexual reproduction known as "Muller's ratchet" [7]. According to this explanation, genetic exchanges prevent the accumulation of deleterious mutations by eliminating linkage disequilibrium, i.e., creating genotypes devoid of mutations. This theory was developed in a mathematical model by Kondrashov [8], in which genetic recombination generates combinations of deleterious mutations that are eliminated by truncating selection.

According to the genetic model termed by Bell "the Tangled Bank" after Darwin's metaphor in the concluding paragraph of *The Origin of Species*, sexual reproduction generates a diversity of genotypes, which provides for adaptation of organisms to spatially changing environments. In accordance to the so-called Red Queen hypothesis, sexual reproduction, creating various allele combinations, ensures successful competition with related species and, primarily, protection against parasites [4, 9, 10]. A similar model, known as "Best Man or Lottery," emphasizes the fact that genetic exchange generates individuals with maximum fitness through combining advantageous mutations [4].

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Comparison of properties of primitive and higher species (after Zavadsky [23])

Species group	Number	Mean survival	Fecundity	Body size	Longevity
Primitive	Very high	Very low	Very high	Microscopic	Very low
Higher	Low	High	Low	Large	High

Thus, it seems that by now there is no shortage of diverse explanations for the advantage of sexual reproduction. Nevertheless, reviews devoted to this subject [11, 12] generally state that it is still impossible to determine "empirically," which of the proposed models describes the actual situation in nature and that the reason for the wide occurrence of obligate sexual reproduction remains unclear. The authors of a recent extensive review [13], containing a detailed analysis of various models of sexual reproduction, came to a startling conclusion that all of the models considered by them can to some extent (?!) explain the role of sexual reproduction. In this view, a suspicion arises that the authors of the models suggested earlier did not take into account an important aspect significant for understanding the necessity of genetic exchange.

Indeed, as we have shown [14, 15], this problem can be clarified on the basis of more careful analysis of the notion of fitness, which is typically used for estimating recombination effects. The fact is that fitness, measured as a rate of propagation, is generally decreased by recombination owing to genetic load [16, 17]. However, such an important fitness component as viability (survival) requires genetic exchange to be maintained at a sufficiently high level, since genetic exchange generates valuable genotypes. Based on this, in particular, we define viability as a trait differing from fitness, namely, as ecological resistance of organisms [18–20]. As follows from the cited works, viability of organisms under conditions of their prolonged existence in the ecological niche of the species depends on their ecological resistance, or the ability to withstand adverse external factors. This property of organisms depends on the presence in their genomes of complete sets of adaptive, or "nonessential" genes, which are normally inherited both as plus and as minus alleles. In our previous papers [18, 20], we referred to nonessential genes as adaptive. They can also be named genes of ecological resistance. The presence of such genes in genomes ensures adaptation of organisms to specific conditions of their ecological niches. For instance, the presence of thorns in plants or protective coloration in animals defend the organisms from their natural enemies, although the absence of these characters as such does not cause the lethal effect. This example shows that "nonessential" genes in fact can play a very important role in survival of organisms in their environment.

At the same time, many genes of ecological resistance may contribute very little to the viability of individuals, influencing their survival only under special, uncommon conditions.

Genetic exchange restores complete sets of plus alleles of genes of ecological resistance, lost through mutations, thereby restoring a high level of ecological resistance.

TWO MAIN PARAMETERS CHARACTERIZING THE EXISTENCE OF SPECIES

Before considering the problem of the importance of genetic exchange for the existence of species, one should clearly understand, what is life as the means of existence of organic bodies, which are themselves rather unstable. It is well known that this means of existence of organic bodies includes, first, the ability of these bodies, i.e., organisms, to exist and develop as integral entities under certain environmental conditions, and, second, their ability to reproduce, i.e., to produce new organisms like themselves. Apparently, the rate of reproduction of new organisms must be inversely related to the life span of the organisms, i.e., the time of their existence in the given environment. If the rate of appearance of new organisms is not sufficiently high, their existence may be interrupted because of the limited life span of the initial, parental organisms.

Thus, the possibility of more or less prolonged existence of organisms of any species depends, on the one hand, on their life span, and on the other, on the number of progeny produced during their lifetime. This simple reasoning best clarifies the point that two different parameters are needed to characterize the ability of biological species to exist. One of these parameters reflects the ability of the organisms to exist for a period of time that is sufficiently long to produce progeny; the other, their ability to produce enough progeny during their lifetime, so that the total number of the organisms does not decrease in each subsequent generation. The ability of organisms for sufficiently long individual existence may be defined as the average survival of individuals or the probability of the participation of the individual in reproduction of the species. It is this parameter that was termed ecological resistance [14, 15].

Thus, to characterize the ability of organisms of different species to exist, two different parameters should be used: first, the probability that the individual, after being born, will have time to produce progeny, and, second, the reproduction rate, i.e., the rate at which the organism can produce progeny. The former of these basic parameters of existence of living organisms is their ecological resistance, while the latter is their fitness. Regrettably, in most genetic studies, description of population number dynamics until recently has

involved only one parameter referred to as fitness, which combines two qualitatively different characteristics.

The prominent Soviet evolutionist Zavadsky was the first to notice that in nature, the progress is achieved in two different ways: on the one hand, by increasing average fecundity and, on the other, by increasing average survival of an individual [21, 22]. Zavadsky pointed out that highly organized species are mostly characterized by an increase in individual survival with concurrent enhancement of life span [14] (see the table). In the context of the proposed notion of ecological resistance, the evidence from Zavadsky's table suggests that on the macroevolutionary scale, biological progress is achieved by increasing ecological resistance of the species, while primitive species, which stay on low stages of vertical evolution, often use only one way to adapt to changing environments: enhancing their ability to produce more progeny, i.e., increasing fitness.

Defining ecological resistance as the average survival of an individual sheds light on the fact that this property of organisms determines their ability to withstand adverse environmental factors, endangering the existence of the species. Thus, although the potential biologically possible lifespan of a species may be long, the average survival and, correspondingly, ecological resistance of this species can stay low. For instance, in such arboreal species as sequoia, pine, oak, lifetime can exceed hundreds of years, but the probability of seed survival may be low. Consequently, ecological resistance of these tree species remains relatively small.

In higher animals, the relationship between the average lifespan and ecological resistance is more pronounced. In them, longer lifetime generally correlates with higher survival, i.e., higher ecological resistance. In this case, a biological paradox arises. From the mathematical viewpoint, the probability of successful completion of the ontogeny and reaching sexual maturity is the higher the shorter is the lifespan. However, in actuality the probability of successful completion of the ontogeny is greater in higher species, which have more intricate organization, and thus longer development.

In Fig. 1, life cycles of primitive (bottom) and highly organized (top) sexually reproducing organisms are shown schematically as horizontal arrows of different lengths. Each life cycle is terminated by reproduction and production of progeny (eggs, embryos, seeds, etc.), which is depicted as a hatched circle. The circle area corresponds to the number of progeny, and the length of the arrows, to the time of reaching sexual maturity. This time also reflects ecological resistance of the organism, since longer ontogeny requires the development of more efficient systems of organism protection against adverse environmental factors. Figure 1 shows that the ecological resistance does not increase during the relatively short microevolutionary processes, although fitness can increase through an increase in fecundity. A qualitative change in the biological organization that leads to higher ecological resistance results from macroevolutionary development, since it requires a preliminary formation of new genes and new regulatory DNA sequences. Ecological resistance of an organism (P) can be defined as $P = e^{-r\tau}$, where τ is the time required for participating in reproduction and r is the minimum value of the relative reproduction rate per individual (Malthusian parameter), needed for the existence of organisms with the ecological resistance P [14, 20].

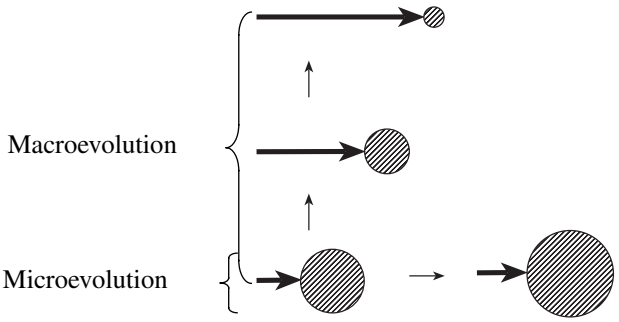

Fig. 1. Diagram of an increase of fitness in microevolution and an increase of ecological resistance in macroevolution.

In expression $P = e^{-r\tau}$, higher values of reproduction rate r and lifespan τ mathematically correspond to lower values of probability P. Primitive species, indeed, exhibit correlation between high values of reproduction rate (and high fecundity) and low probability of individual survival (see the table). As to lifespan τ, here we see the biological paradox mentioned above: from the mathematical viewpoint, the probability of successful completion of individual development is inversely related to the duration of development. However, in the biological context, a reverse relationship is true: in higher organisms, longevity increases with increasing the probability of survival P. This is explained by the fact that fluctuations of adverse environmental conditions, decreasing the actual value of P, are compensated not only by higher fecundity, i.e., reproduction rate r, but also (especially in higher organisms) by longer lifespan τ. In this case, longer development is usually a consequence of more complex biological organization, which permits the organism to overcome the effects of adverse environmental factors.

However, a "traditional" way of overcoming the effects of adverse environmental factors is an increase in fecundity and thus in reproduction rate r. A population that can not constantly increase the reproduction rate via increasing fecundity would not be able to exist in real, constantly changing environments for a long time, since probability of survival P depends not only on the properties of the organism itself, but also on fluctuations of the effects of adverse environmental factors. Because of this, the actual reproduction rate r, determining the organism fitness, usually increases during evolution. Populations with not sufficiently high r (par-

ticularly primitive species with low *P*) will go extinct in the periods, when the effect of deleterious external factors is especially great. Populations with high *r*, i.e., high fecundity and thus high reproduction rate, will eventually be overcrowded in the periods of low effects of adverse environmental factors. This explains discontinuous evolution and subsequent evolutionary bursts, since consequences of overcrowding crises are similar to those of radical changes of environments of populations and species. As shown by us earlier [20, 24, 25], overcrowding crises trigger processes, leading to specialization and terminating by an appearance of forms with higher ecological resistance.

The opposition of fecundity and survival of individuals in evolution, pioneered by Zavadsky, is reflected in the existence of two types of natural selection: r-selection and K-selection [26, 27]. As is well known, r-selection operates under conditions of the organisms filling a free ecological niche and is directed at intensifying reproduction, whereas K-selection occurs under conditions of a filled ecological niche and is actually directed at increasing survival, i.e., ecological resistance of the individuals. However, it should be taken into account that in microevolutionary processes, K-selection can only restore the high level of ecological resistance, ensured through genetic exchange among individuals. K-selection itself cannot produce new genes and new functions, essential for significant increase of the ecological resistance and the formation of new taxa on this basis.

GENES FOR ECOLOGICAL RESISTANCE AND THE ROLE OF DIPLOIDY

The resistance of an organism to adverse environmental factors that can cause its death (such as predators, parasites, deleterious climatic fluctuations, starvation) depends, in particular, on the set of genes for ecological resistance (nonessential genes) that this organism has. This category include genes whose damage does not always lead to lethality. These genes usually constitute the majority in the species genome. They ensure ecological resistance of an individual, i.e., its survival upon altered environmental conditions. Many genes of ecological resistance provide survival of an individual only in extreme, rarely occurring conditions.

Under standard conditions, genes of ecological resistance typically are not expressed, which explains their presence in the genomes as both plus and minus, or null, alleles. That is why under standard conditions, mutations damaging genes of ecological resistance also are not expressed, though their accumulation inevitably leads to a decrease in ecological resistance. In this connection, accumulation of mutations in silent (under standard conditions) genes of ecological resistance can be compared to the accumulation of mutations inactivating one of two copies in duplicates of constantly expressed genes, formed upon polyploidization. In such cases and in tandem duplications of separate chromosome segments, there is theoretically a possibility of total damage of one of the two genes and preservation of the gene function [28, 29]. According to [30, 31], the time needed for fixation of a mutation at one of two duplicate genes is approximately equal to $1/\mu$, where μ is the rate of mutations (inactivating the gene) per gene per generation. If we take $\mu = 10^{-5}$, one of the two duplicate genes is inactivated in 10^5 generations. This time is substantially higher only in populations of a very large size [30, 31].

However, practically identical genes in duplications may also gradually accumulate small mutational lesions. In this case, referred to as subfunctionalization [31, 32], the original duplication is preserved, but the combined activity of the two genes drops to the level of one gene. Somehow or other, as to genes of ecological resistance, which operate only in some periods of time, they, like "redundant" genes in duplications, can accumulate (pseudo)-neutral mutations in ordinary environment of the species. However, such mutations will sooner or later manifest at the level of ecological resistance of the organism as a decrease in the ability of exist in the ecological niche of the species for a relatively long time. Even relatively small damage of genes of ecological resistance may be expressed as low survival, e.g., in the drought season under starvation or in winter because of low winter hardiness, etc. What is usually implied by the Darwinian "struggle for survival" is in essence ecological resistance of the organism, i.e., its capability to counteract the effect of diverse "killing factors" of the environment. For instance, even under normal environmental conditions, genes of ecological resistance from time to time operate during the period of the development prior to reproduction, which allows the organism to successfully overcome the consequences of diverse stresses of random origin. Therefore, in the absence of a sufficiently complete set of such genes, the organism may not survive to reproduction, which is equivalent to a reduction in effective population size.

Populations of a very large size probably can resist accumulation of mutations damaging genes of ecological resistance and mutations damaging the expressed genes in duplications [30, 31]. In such populations, the fixation of newly arisen mutations occurs very slowly, and individuals maintaining high ecological resistance can be preserved only through stabilizing ("negative") selection. However, in populations of a limited size, only genetic exchange, restoring high viability in a part of the progeny, can counteract the accumulation of mutations in genes of ecological resistance. This conclusion is supported in nature primarily by the universal occurrence of genetic exchange, which is found at all levels of biological organization, from viruses to higher organisms. For instance, for the RNA virus $\varphi 6$, there is evidence indicating an existence of a mechanism of mutation accumulation in the absence of recombination, which is similar to "Muller's ratchet" upon the population passing through a bottleneck, i.e., under

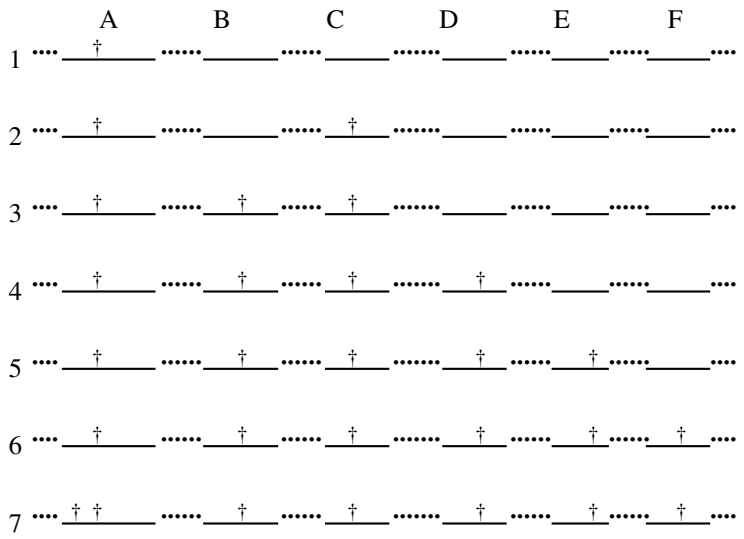

Fig. 2. Accumulation of mutations in "silent" genes of ecological resistance (B, C, D, E, F) during positive selection for changing the A gene function (after [20]). The consecutive stages (1–7) of mutation accumulation are shown by crosses.

conditions where its size is greatly reduced [33]. Similar data were obtained for bacteria [34].

A complete rejection of sexual reproduction and transition to parthenogenesis occurred in the Bdelloidea family and in some crustaceans, organisms that nonetheless have existed during tens of millions years (see [35] for a review). These animals are typically very small in size. For example, size of members of the family Bdelloidea ranges from 0.1 to 0.5 mm. This small body size is likely to mediate achieving great population numbers, which may promote preserving and selecting individuals with high ecological resistance. A possibility of transfer of genetic information among individuals within a population via viruses also cannot be excluded, but so far there is no evidence indicating that. In addition, it should be taken into account that these organisms are diploid.

Having spread at the early stages of evolution, diploidy has gradually transformed genetic exchange into periodic uniting of haploid genomes of an independent origin.

This is, in particular, indicated by the preserved diversity in the haploid phase/diploid phase ratio in the life cycles of lower plants. In higher plants, the haploid phase is preserved in the form of the embryonic sack. Genetic exchange as such, by crossing over or chromosome redistribution, is reduced to a stage of gametogenesis occurring in the same organism. In diploids, owing to complementation, i.e., mutual compensation of defects of two haploid genomes, the organisms in each generation have a more complete set of genes of ecological resistance and thus maximum ecological resistance. Because of diploidy, the need of constant genetic exchanges in more primitive (diploid) organisms became less acute. This is even more relevant for polyploids. It is no coincidence that the transition to various types of apomixis in many species of such genera as *Hieracium, Rubus, Poa, and Taraxacum*, is usually accompanied by polyploidization [36, 37].

THE SIGNIFICANCE OF GENETIC RECOMBINATION FOR EVOLUTION OF SPECIES

The fact that genetic exchange promotes the elimination of minus alleles of genes of ecological resistance is only one side of the coin. The other, equally important aspect of sexual reproduction and genetic exchange concerns evolution of organisms and thus is directly related to the Fisher–Muller theory considered above. According to one of the postulates of the biological evolutionary axiom (BEA), which we have formulated earlier [38], "evolution of the organic world would have been impossible without genetic recombinations or analogous events."

BEA is based on an assumption that novel genetic information cannot be generated within a genome only by means of selection without losing an equivalent or even greater amount of original information in the individual subjected to selection. Hence, genetic exchange is absolutely necessary for the newly generated information to be used in the subsequent evolutionary development of the species. The fact is that the formation of a new gene or a new nucleotide sequence requires an accumulation of nucleotide substitutions in a definite, short DNA region. The sequential formation and then fixation of even two mutations in the same DNA region is an unlikely event. Thus, these events will inevitably be accompanied by concurrent fixation of other mutations, neutral under the given conditions of selection (Fig. 2).

BEA partly includes the postulate of Muller on the inevitable genetic degradation of asexual populations

owing to the mutation accumulation [7], but this axiom is based on the fact that genes of ecological resistance of an organism are not expressed under environmental conditions standard for this organism and that mutations in these genes are inherited as neutral. However, the main significance of BEA lies in the fact that in the absence of genetic exchange, it is impossible to combine genetic information that was created by positive selection in different populations or different intraspecific taxa, in one individual.

Speaking about uniting advantageous mutations, Fisher [5] and Muller [6] ultimately implied the union of new, beneficial alleles. However, in the early 1930s, lacking real understanding of the nature of genes and mutations, these authors could not speak in terms of genetic information. Fisher wrote that sexual reproduction has a fundamental significance for the theory of evolution; he also pointed out beneficial changes in different structural elements of the germplasm, which would be lost in asexual organisms, because they would occur in individuals not destined to contribute to the ultimate progeny of the species [5, p. 160]. Muller [6] also supposed that the primary function of sexual reproduction is creating novel, evolutionarily valuable gene combinations.

Crow and Kimura [39], as well as the authors of many later studies, in their analysis of the Fisher–Muller theory overlooked its potential biological significance, because they in fact confined themselves to determining the probability of mutation fixation in sexual and asexual populations. Only Bodmer [40] showed an adequate understanding of the Fisher–Muller theory. In particular, this author came to a conclusion that the advantage of genetic recombination is positively related to the population size. In contrast to all other authors, Bodmer determined the probability of combination of two given mutations, i.e., the already existing advantageous alleles, in the same genome (see [41]). In any case, distinguishing the notion of ecological resistance, which depends on the operation of a set of periodically expressed genes, from a vague notion of fitness allows one to clearly see the uniting, or synthetic function of genetic exchange. In this case, synthesis is implemented at the level of new genes, i.e., new genetic information formed by positive selection in various populations of the species. Thus, from the biological viewpoint, the central place among various explanations for the role of genetic recombination is occupied by the Fisher–Muller theory, not only in its historical aspect, but also as a theory pointing to the fundamental significance of genetic exchange in evolution.

CONCLUSIONS

Vagueness of the notion of fitness has been noted by many authors [42, 43]. Stearns [44] remarked that fitness is "something everyone understands but no one can define precisely." The intuitive understanding of the notion of fitness seems to imply that fitness is something that ensures maintaining population size at a sufficiently high level. Defined in this sense, fitness must depend first, on fecundity, and second, on survival, or ecological resistance. However, here survival is of primary importance, because exactly survival determines the number of progeny preserved to the completion of the life cycle and able to produce new progeny. Accordingly, defects of ecological resistance are expressed as reduction in population size in each new generation, threatening the existence of the species. This implies the necessity of genetic exchange, or sexual reproduction, in each new generation, particularly in highly organized species with low fecundity. Fecundity, which ensures an advantage of a clone, genotype, strain, etc., under conditions of population growth, traditionally measured by Malthusian parameter [5], historically may be closer to the notion of fitness. Ecological resistance, characterizing the ability of population not to grow, but to survive under conditions of reduction of population size, is the flip side of the coin. It is ecological resistance that requires restoring (even in part of the progeny!) in each generation through genetic exchange. As to fecundity, which depends on a concerted functioning of many genes, its increase requires a gradual accumulation of regulatory mutations, while genetic exchange of genes taken from different genetic backgrounds, is usually harmful. This biological truth is supported by well-known cases of low fecundity in hybrids.

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