GENETIC DIVERSITY AND DIVERSITY OF ENVIRONMENTS

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1. Introduction

Like many ignorants, I have my deep respect for mathematics tinged with a kind of superstitious awe. Using their recondite, and to me inscrutable methods, mathematicians reach conclusions about problems of genetics and evolution, which I must humbly accept as following inexorably from the premises and the assumptions made. I hope, however, I am not being impertinent if I say that not all of these conclusions are always convincing. The difficulty stems from the premises and the assumptions. Most exasperating is the habit of certain mathematical geneticists who make their assumptions implicit rather than explicit, on the ground that to them the truth of their assumptions seems self-evident. I have accepted the kind invitation of Professor Neyman to participate in this Symposium with reluctance, because of my ignorance of mathematics; all I can talk about are certain self-evident, and certain not so self-evident, biological premises and assumptions.

Let us restrict our attention to Mendelian populations. Mendelian populations are reproductive communities of sexual and either obligatorily or at least facultatively cross fertilizing organisms. This leaves out of account the asexual, exclusively self-fertilizing, parthenogenetic organisms, as well as some intermediate situations in which cross fertilization is rare. A Mendelian population is said to have a corporate genotype or gene pool. The gene pool of a population may be envisaged as the genes in the array of the gametes, sex cells, which give rise to the following generation. The composition of the gene pool can be described in terms of the numbers or of the frequencies of the genes and linked gene complexes. The mechanisms of the replication of the hereditary materials tend to make the gene pool constant generation after generation. Mutation, recombination, selection, sampling errors in small populations, vicissitudes of the environments, and variations of the reproductive habits and opportunities are liable to change the composition of the gene pool.

2. The classical model

Let us begin with a model which is probably the simplest, thoroughly unrealistic biologically, tractable mathematically, and, therefore, the favorite with some mathematical geneticists and genetical mathematicians. Assume a Mendelian population for which (a) the environment is constant in time and in space for all members of the population; (b) the variable gene loci are each represented by two or more alleles, one allele being "normal" and beneficial in the environment, and all other alleles more or less disadvantageous in homozygotes; (c) most of the gene loci are occupied by identical alleles in all individuals, the variable loci are a minority; (d) the genes produce their effects each independently of the others; epistatic interactions, especially as concerns fitness, do not occur or are negligible; the fitness variations caused by the alleles at the unfixed loci are simply additive or multiplicative; (e) the population size is infinite or large enough to be treated as such.

Genetic uniformity is clearly the ideal state under the above model. Natural, artificial, or eugenic selection should eliminate all disadvantageous genotypes, and establish the single optimal homozygous genotype. All members of the population will be genetically identical, and all optimally fit. This paragon of adaptive virtues is difficult to achieve because of mutation. In the absence of known means to suppress all mutation, genetic variants, all or nearly all deleterious, will be injected into the gene pool in every generation. The fitness of the population will always lag below the optimum. How far below will be relatively easy to determine. If the mutation rates and the loss of fitness caused by each mutant are known, the genetic equilibria of the mutants can be predicted. The magnitude of the genetic load which a population carries can be estimated, as well as the numbers of the "genetic deaths" which the population will suffer. These numbers can be made as frightening as you wish, especially if you forget to state that a genetic death does not always produce a cadaver. Having no children makes you genetically dead, having one child makes you genetically half dead.

The model outlined makes all genetic diversity unwelcome departure from the ideal optimal uniformity. Is it at all conceivable that this Platonic archetypal state may ever be achieved? It is conceivable, but at a cost of truly heroic measures. The first is abandonment of sexual reproduction. A technique may conceivably be invented to stimulate the development of human diploid cells from a tissue culture to yield embryos and eventually adult bodies. Such a feat has indeed been accomplished with cells of a lowly plant, the wild carrot. Assuming, then, that one encounters and recognizes the carrier of the optimal genotype of the species, obtains a tissue culture of his cells, avoids all mutation, makes the cells develop without meiosis and fertilization, and accepts the genetic identity as not unbearably dull, then the "ideal" mankind, or any other species, is conceivable. This ideal is implicit in some eugenical writings, although their authors explicitly disclaim the advocacy of any such ideal.

3. Requirements to be met by a more realistic model

3.1. *Heterotic balance.* Suppose now that some gene loci produce more than a single beneficial allele. Overdominance makes the heterozygote A_1A_2 not intermediate between, but more extreme than the corresponding homozygotes, A_1A_1 and A_2A_2. Hybrid vigor or heterosis may result in A_1A_2 being fitter than A_1A_1 and A_2A_2. Balancing natural selection will then maintain both alleles, A_1 and A_2, in the population, with frequencies depending on the relative fitnesses of the homozygotes. This heterotic balance model is considerably more complex than the simplest classical model discussed above. A population may have many unfixed gene loci, at which the fittest genotype is a heterozygote. Assuming, as before, that the contributions of different genes to fitness are additive, the optimal genotype is heterozygous for all heterotic loci and homozygous for all classical loci. There will, however, be a genetic diversity, individuals heterozygous for from zero to n heterotic genes being represented with certain frequencies. This diversity will be maintained not by the mutation pressure, as in the classical model, but by the heterotic balancing selection. A population consisting entirely of multiple heterozygotes cannot be achieved with sexual outbreeding, because relatively ill adapted homozygotes will arise in every generation. It can, however, be achieved by a genetic *tour de force;* certain apogamous plants produce seeds without fertilization, and all seeds have the same genotype as the mothers.

How prevalent and widespread is heterotic overdominance in natural populations is a problem on which no agreement has been reached among geneticists. That heterotic genetic variants do exist is beyond dispute; some geneticists contend, however, that such variants are rare, and that the simple classical model is a fair approximation. Others argue that heterotic balanced polymorphism at many loci is not uncommon. This necessitates a more complex model of the genetic population structure. Anyway, it is clear that experimental geneticists need help of their mathematical colleagues, both in construction of theoretical models and in planning experiments to discover what is the real situation in populations of different organisms. Professor Levene whose article [20] follows the present one, and also Band [1], [2], Crenshaw [6], Crow [8], Dempster [10], Kimura [15], [16], Lerner [17], Li [29], [30], [31], Morton [33], Sanghvi [41], Schull and Neel [42], Wallace [46], and others have made many valuable theoretical as well as experimental contributions in this field. The problem, let me repeat, remains nevertheless wide open and unsolved.

3.2. *Diversity of environment and selection.* To be at all realistic, the genetic models of population structure must take the diversity of environments into account. Certain parasites which inhabit the blood stream of warmblooded vertebrates are probably the organisms living in the most uniform environments that exist outside of some specially equipped laboratories. Even blood parasites have to face environmental changes when they are infecting new hosts, and probably also in different parts of the host's body. Other organisms face radically different environments at different seasons, warm versus cold in temperate and cold climates, wet and dry in the tropics, or at different stages of the life cycle (think of the larvae and the adults of many insects), or in different parts of the geographic distribution of the species, or in different habitats within the same geographic locality. The environmental changes may be cyclic and recurring regularly within a single generation of an organism or in different generations. Seasonal changes are an obvious example. Or, they may be recurrent in space rather than in time, as with different food plants or other food sources that may be present in a locality in which a population dependent upon these food sources lives. This situation is sometimes described as the occupation of a variety of ecological niches by a population. Some species of organisms and some populations have a greater and others a more limited variety of ecological niches available to them.

Abandonment of the assumption of environmental uniformity, and substitution of environmental diversity results in models of population structure that are uncomfortably complex and relatively intractable. These are good reasons why mathematicians as well as geneticists are reluctant to deal with them. Unfortunately, nature has not been kind enough to make all things as simple as we would like them to be. Complexities have to be faced. We know much less about population genetics than is still unknown. To pretend otherwise is to retard acquisition of more satisfactory knowledge. Among the colleagues participating in the present Symposium, Bodmer, Dempster, and Levene have made some pioneering studies of the consequences of environmental diversity; they will not consider my saying that they have barely scratched the surface an impertinence.

There are, in general, two ways of being adapted to environmental diversity. One is physiological or developmental homeostasis. The other is genetic diversification, in which different genotypes within a population, or different populations, are adaptively specialized to fit different ecological niches or different environmental contingencies. Maintenance of a constant body temperature despite temperature changes in the environment is a good example of physiological homeostasis; dependence of the body size in adult insects on the amount of food available to nymphs or larvae is an instance of developmental homeostasis. Presence in a population of genetic variants with different food preferences, different temperature tolerances, and so forth, permits a fuller utilization of the environmental opportunities than could be achieved by a single genotype.

Brazenly opportunistic, evolution utilizes homeostatic plasticity as well as genetic specialization and diversification to achieve adaptedness in its creations. Is either of these methods superior to the other? It is intuitively obvious that a genotype which could react to every environment by producing optimal phenotypes would be ideal. This would, indeed, be that will-o'-the-wisp invented by some geneticists, the optimal genotype. Ours is, however, not only not the most perfect of all conceivable worlds but not even the best of all possible worlds. The adaptive capabilities of every genotype are circumscribed, more or less widely or narrowly. This makes adaptation by means of genetic diversification sometimes preferable. In general, the more diversified is the environment the less likely is a genotype fit to occupy all the available ecological niches. The problems that arise are those of evolutionary strategies. Mathematicians and geneticists can play imagining themselves being gods, and decide what strategy evolution could have used to achieve adaptedness most rapidly and effectively. The optimal strategy would, of course, yield the most perfect possible adaptedness of a population to its environments. Such a strategy could, conceivably, rely on a homeostatic plasticity given by a single or a few genotypes, or could make use of an adaptive genetic polymorphism, or various combinations of these methods. Levins [22], [23], [24] and Lewontin [26], [27], have produced very interesting studies of optimal evolutionary strategies. There evidently exist many fascinating and challenging problems in this field, both for theoreticians and for experimentalists. One may inquire how evolution could be made adaptively most productive, and one may wish to find out whether evolution has in actuality utilized anything resembling the methods which our mathematical and biological wisdom indicates as most advisable.

Recognition of the importance of environmental diversity necessitates consideration of some forms of selection which are rather more complex than the classical ones. Although they were considered by the pioneers of mathematical genetics, especially by Sewall Wright [47], [48], much remains to be done to achieve a satisfactory understanding, both by way of mathematical models and of their experimental applications. Suppose that there are two or more phenotypes which confer a high Darwinian fitness on their possessors, while the intermediates between them are less fit, or are culled and prevented from reproducing by the breeder. This is diversifying selection, which will tend to make the population genetically variable or polymorphic. (It is also termed "disruptive" selection, which is a most unfortunate choice of word, since this selection is biologically constructive rather than disruptive.) One of the situations in which diversifying selection will occur is when the fitness of a genotype is a function of its frequency; in other words, the selection coefficient s is a function of the gene frequency q.

An interesting, though perhaps rather special, example of this is the advantage in mating of a type which is rare, and disadvantage of a type which is common in a given environment. In the experiments of my colleague, Dr. Lee Ehrman [13], females and males of two strains of *Drosophila pseudoobscura* are introduced into an observation chamber, and the matings that occur are recorded. The following data were obtained using strains derived from wild flies collected in California (C) and flies collected in Texas (T). The numbers of the flies of each sex per chamber, the numbers of females and of males that mated (of course, in several chambers), and the chi squares (one degree of freedom) testing the deviation from randomness of mating, are summarized in table I.

In Drosophila, males court all females rather indiscriminately, but females accept only some and reject other courtships. Observed courtships are several times more numerous than copulations in the observation chambers. Now, with C and T females and males being equally numerous in a chamber, the C and T flies mate about equally frequently; when C are four times more numerous than T, the number of C males copulating is only twice that of T males; when

TABLE I

MATINGS OF DROSOPHILA PSEUDOOBSCURA
Numbers of flies of each sex per chamber,
the number of females and males that mated,
and test for randomness and mating.

Flies per Chamber	Have Mated				Chi Squares	
	C ♀	*T* ♀	*C* ♂	*T* ♂	♀	♂
12 *C* + 12 *T*	50	54	55	49	0.15	0.39
20 *C* + 5 *T*	84	25	70	39	0.59	16.96
5 *C* + 20 *T*	30	74	39	65	5.10	19.91
23 *C* + 2 *T*	93	8	77	24	0.00	34.75
2 *C* + 23 *T*	12	88	30	70	2.17	65.76
10 *C* + 15 *T*	60	69	39	90	2.28	5.13

T are four times more numerous than *C*, about a third of the copulating males are *C*; with *C* being eleven times more frequent than *T*, or vice versa, the success of the males of the rare type is even more striking. As to the females, the numbers mated are either in proportion to the frequencies of a given type in the observation chambers, or else the rare type has an advantage, less striking, however, than the advantage of the rare males.

The physiological basis of the greater mating success of the rare males is unknown. The genetic consequences of such phenomena are, however, evident enough. The genes which induce this behavior will increase the Darwinian fitness of their carriers when they are rare and decrease it when they grow more common. The diversifying selection will then operate to bring about a balanced polymorphism without any heterosis in the heterozygotes. The gene frequencies will reach equilibria when the mating efficiencies of the different genotypes become equal on the average. The sexual advantages may compensate for some disadvantages in other traits influencing fitness. This is observed in the experiments of Dr. Ehrman on the mating behavior of the mutant orange eyes, compared to that of the wild type. Orange flies of both sexes are somewhat weaker than flies with the normal eye color; when orange males are less frequent than wild, their mating proficiencies become, however, equalized. A quantitative theory of such phenomena remains to be worked out.

A negative relationship between the genotype frequency and the Darwinian fitness need not be restricted to mating success. It almost certainly occurs in nature when a Mendelian population contains two alleles, A_1 and A_2, which make their carriers more viable, or more fertile, or otherwise more fit when they use different foods, or different resting or nesting or hibernating places, or are otherwise differentially adapted to different conditions which the environment offers. Diversifying selection will then favor a genotype when it is rare and discriminate against it when it is common. Although as a theoretical possibility this is attractive enough, so little attention have geneticists, ecologists, and other biologists given to this possibility that I am unable to find in the literature a convincing case that could be used here as an illustration.

There are, to be sure, excellent data of Birch on three species of the grain beetles *Calandra* and the related genus *Rhizopertha,* of Park [34] and his school and of Lerner [17] and his colleagues on two species of the flour beetles *Tribolium,* and of Moore [32] on two species of *Drosophila.* In all these studies, it has been found that one species is better adapted to a certain food, or to a certain temperature or humidity than the other species, while this latter is superior under different conditions. In mixed populations one or the other species is usually the winner, depending upon the environment. Most fascinating are the recently published experiments of Sokoloff, Lerner and Ho [43] on mixed cultures of *Tribolium castaneum* and *T. confusum.* The first of these does better than the second on wheat flour, while the second does better in cornmeal. When in competition on corn, *castaneum* is, however, the winner as long as *confusum* is also present, but when the competitor is eliminated, the winner goes into decline too. The solution of the puzzle is that these beetles are cannibals, and while suffering from a nutritional deficiency on corn, *castaneum* is able to supplement its diet by eating developmental stages of *confusum.* When the supply of the latter species is exhausted, the species practicing "xenocide" commits unwitting suicide.

In humid tropics, where there are many species of *Drosophila* developing in fermenting fruits, Pipkin [40] and others found a remarkable differentiation of ecological preferences. Although most species of *Drosophila* can feed on most species of fruits, each *Drosophila* has a certain repertory of fruits which it chooses if choice is available. This is an admirable arrangement, because when there is a choice of fruits, different *Drosophilae* go after different fruits, thus minimizing competition. The preference does not, however, reach the point when a *Drosophila* could develop only in a single kind of fruit; so rigorous a specialization would evidently endanger the continuation of the species if its food source were owing to some accident temporarily unavailable. Differential food preferences almost certainly exist within species as well, but the evidence for this is circumstantial and inconclusive.

The evolutionary situations which arise when a Mendelian population faces a diversity of environments have been surprisingly neglected by biologists, and perhaps because of this neglected also by mathematicians. Environments may vary in time, or in space, or both. Variation in time may be regularly cyclic, as with seasons, or irregular, like wet and drought years. Variations in space may recur mosaic fashion, as meadows, forests, and hill slopes in many countries, or may be more systematic, as with the rainfall becoming greater or more scarce as one approaches the ocean or ascends to higher altitudes in the mountains. How will the population genotypes respond to these challenges? Under what conditions will stably balanced polymorphisms be established? In a two page article published some 13 years ago, Levene [18] has shown that when two or more ecological niches are available, two or more alleles may be held in stable polymorphic equilibria, without the heterozygotes being heterotic. Dempster [10], Li [29], [30], Lewontin [25], [27], [28], Haldane and Jayakar [14], Parsons [35] to [39], and others have discussed Levene's and some other models. The "polymorphism due to selection in varying direction" examined briefly by Haldane and Jaykar seems particularly interesting, although it remains to be discovered how often the biological situation postulated by them is encountered in nature. They assumed a pair of alleles, one of which is dominant and the other recessive, each of which makes its carrier fitter than its counterpart in different generations. Now, if the arithmetic mean of the fitnesses of the recessives in different generations is greater than unity, while the geometric mean is lower than unity, both alleles will persist in the population owing to this form of balancing selection.

Very little attention has been given to the effects of epistatic interactions of different genes affecting fitness. That such interactions occur, both for loci in different chromosomes and for linked loci, is not denied by anyone; how prevalent epistatic phenomena are in reality is, however, an open question. I leave it to you to judge whether it is advisable to build theories of population genetics ignoring epistasis. Bodmer and Parsons [5], Lewontin and Kojima [28], and some others have made theoretical studies of the situations that may arise when linked genes affect fitness differentially when in coupling and when in repulsion phase. As far as I know, epistasis by itself, without linkage or heterosis, has not been shown to yield stable polymorphisms. The situations that might arise when diversifying selection operates with epistatically interacting loci are, however, in need of investigation.

4. Concluding remarks

I realize how unsatisfactory this article may appear to you. I have tossed before you a host of problems, and have given no solution for any of them. To give solutions was, however, not within my ambition, because this is beyond my capabilities. The intention was rather to ask the mathematical colleagues for help, which geneticists and evolutionists are so much in need. The classical model of genetic population structure has until recently received the lion's share of attention. It has the advantage of simplicity, but the disadvantage of misrepresenting reality. It is not entirely played out, and probably never will be, since it does contain a grain of truth—for some genes and for some environments its simplifying assumptions are satisfactory as approximations. But the biological reality is different, and if I may say so, more interesting than the classical model suggests. Natural populations of many sexual species, including man, contain so much genetic diversity at so many loci that two individuals probably never have the same genotypes, unless they are identical twins. Moreover, a good part of this diversity is not a sad accident, not a departure from this Platonic eidos called the "optimum genotype," but a means whereby the population is adapted to its environments and is able to master additional and new environments. The abandonment of the assumption of uniform environments makes, I realize, your mathematical models uncomfortably complex. Dealing with this complexity is, however, a compelling necessity if we are to understand the biological reality.

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