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Frequency-dependent selection, metrical characters and molecular evolution

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Computer models of selection acting on a quantitative character show that a combination of frequency-dependent and stabilizing selection can maintain many polymorphisms among the genes that determine the character. The models also show that the random order of mutations can give rise to selectively driven stochastic effects that are sometimes more important than random genetic drift. They suggest simple explanations for patterns of divergence between populations and species, and for apparent discrepancies between the rates of morphological and molecular evolution. They point towards a selective theory of 'molecular clocks'.

Introduction

Ever since the great debates between 'biometricians' and 'Mendelians', students of inherited natural variation have followed two separate paths. Population geneticists have studied discrete characters with simple inheritance, and have investigated the dynamics of genotypes. Quantitative geneticists have studied continuously variable characters with complex inheritance, and have been obliged to treat genes statistically as generators of means and variances. They have investigated the dynamics of phenotypes (see, for example, Lande 1980). Because the algebra of population genetics becomes intractable when more than two selectively interacting loci are considered, there has been a large 'no man's land' between the two disciplines. This uninhabited territory includes some areas of great interest. How, for example, do individual loci behave when they contribute to a polygenic character under selection?

The 'no man's land' has lately become habitable. Bigger and faster computers allow us to make models of selection acting on polygenic characters, and to study the behaviour of individual loci. The present paper describes one such study. It was inspired by experiments on predation by birds, but its conclusions have a wider application, and throw light on various phenomena of molecular and morphological evolution.

Allen (1972) offered a quasi-normal distribution of coloured baits (made of flour and lard) to wild garden birds. Nine grades of colour between green and brown were obtained by mixing edible pigments, and the proportion of each colour to be offered was calculated by reference to the normal distribution. Thus the commonest colour was olive (50% of each pigment), and the proportions of other colours fell with increasing concentrations of green or brown pigment. Allen found that the birds disproportionately took the commonest colour, and tended to ignore the rarer ones, despite an initial preference for brown baits.

Shelton (1986) did a similar set of experiments, but used baits that differed in shape rather than colour. A graded series of eleven shapes was offered to the birds. The baits were

cylindrical, varying in length from 1.11 to 3.00 cm in steps of 0.19 cm. All were of equal volume (0.58 cm^3). Once more the birds disproportionately took shapes that were near the mode (2.06 cm in length), and tended to ignore the rarer ones. The disproportion was small, but statistically significant. Shelton then offered the baits in a 'reversed-normal' distribution, where the extreme shapes were commoner than those near the mean. Here the birds took disproportionately more of the extreme shapes, and fewer of those near the mean. Thus the selection was frequency-dependent, not merely disruptive.

Frequency-dependent selection by predators acting on discrete variants is known to be widespread (for reviews see Clarke 1972; Allen, this symposium; Endler, this symposium). However, the studies by Allen (1972) and Shelton (1986) provide, we believe, the first experimental evidence that predators can act in a frequency-dependent manner on metrical variation. When such variation is found in a morphological character it is not usual to consider predation as a factor that can maintain it. Evidently we should do so.

Shape and colour are not, of course, the only characteristics recognized by predators. We can expect that metrical variation in reflectivity, size, smell, taste, sound, electrical properties and behaviour should also be subject to frequency-dependent selection. Nor are predators the only agents of selection that can act in a frequency-dependent manner. Parasites and competitors may be equally important (Clarke 1979; and see papers by Antonovics & Kareiva, Barrett, Christiansen, Levin and Seger, this symposium). Parasites are liable to become adjusted to the modal type of host, and to suffer a disadvantage when they encounter rarer ones. The 'types' in this context could well be values of continuously varying biochemical characters (such as hydrogen ion concentrations, oxidation–reduction balances, concentrations of metabolites, levels of hormones, and so on). Competitors can exert frequency-dependent selection on ecological variables, which may include biochemical adjustments to the environment. For example, alleles at the alcohol dehydrogenase locus in *Drosophila melanogaster* appear to be selected because of their influence on ethanol tolerance, but other loci also contribute to this metrical character (Van Delden 1982).

There have been several theoretical studies investigating the phenotypic effects of frequency-dependent selection on quantitative characters (Bulmer 1974, 1980; Lande 1976; Slatkin 1979) but they have not examined the behaviour of the individual genes that contribute to these characters. If, as now seems likely, this type of selection is common in natural populations, we need to know its effects on the genes. Because stabilizing selection is also common (Endler 1986), models that combine frequency-dependent and stabilizing selection should be particularly interesting.

The models

Our first model assumes a population of 1000 diploid cross-fertilizing hermaphrodite individuals, mating at random. There are five unlinked loci, each with 21 possible alleles, having additive effects on a quantitative character. The alleles are designated *0–20* according to the size of their effect on the character. Thus allele *20* adds 20 units to the character, whereas allele *0* adds nothing. It is assumed that after fertilization the number of zygotes is reduced to 1000 by non-selective (random) mortality, and then the remaining zygotes are subjected to frequency-dependent and stabilizing selection.

The frequency-dependent selective value $W(f)_i$ of a phenotype (i) is calculated as

$$W(f)_i = 1 - Ap_i,$$

where A is a constant, and p_i is the frequency of the phenotype. Because the selective agent may well confuse adjacent phenotypes, we introduce a factor called the 'slop', which is a measure of selective discrimination. The 'slop' factor is the number of phenotypes on either side of the reference phenotype that are confused with it. Thus if the 'slop' factor is 2, the frequency (P_i) is calculated as the frequency of the phenotype itself plus the sum of the frequencies of the four adjacent phenotypes (i+2, i+1, i−1, i−2).

The selective value of phenotype i resulting from stabilizing selection is given by

$$W(s)_i = 1 - \frac{B|i-\theta|}{\theta},$$

where B is a constant, i is the phenotypic value and θ is the optimum phenotypic value. Thus the selective value falls off in direct proportion to the distance from the optimum (in other simulations we allow the selective value to fall off from the optimum in a Gaussian manner, see below).

The net selective value of the phenotype i is taken to be the product of the frequency-dependent and stabilizing components:

$$W_i = W(f)_i \cdot W(s)_i.$$

Mutation is allowed to occur before the next round of fertilization, usually at a rate of 10^{-5}, and then the whole process is repeated. Most of the early simulations were started with the population homozygous for allele *1* at all loci (i.e. with a starting phenotypic value of 10) and with an optimum phenotypic value of 100. Most were run for more than 20000 generations.

Our second model is substantially the same as the first, except that it assumes 32 alleles rather than 21. The programs for both models (the first in Pascal, the second in Fortran) can be obtained from the authors.

We have now done more than 200 simulations, varying the population sizes, the number of loci, the amount of linkage between loci, the numbers of possible alleles, the intensity of frequency-dependent and stabilizing selection, the type of stabilizing selection (linear or Gaussian), the amount of 'slop', the mutation rate, and the initial distance from the optimum. The detailed numerical data will be published elsewhere. We propose here to report some of our general results, and to discuss their implications for evolutionary studies.

Results and discussion

The response of the phenotype

When the values of A and B lie between 0.25 and 1.0, the mean phenotype of the population rapidly approaches the optimum, reaching a distance of two or three units within a few hundred generations. Changes in the mean phenotype, however, do not reflect the whole of the evolutionary change. Adjustments of the variance often take as much as fifty times longer. These adjustments bring about an appropriate balance between the opposing forces of stabilizing and frequency-dependent selection. Once this balance has been reached, the variance remains approximately constant. The final size of the variance depends on the relative strengths of the two kinds of selection.

When the values of A and B are small, the whole process takes longer, but the results are qualitatively the same.

The response of the genotype

When linear stabilizing selection acts alone, the population eventually either becomes completely monomorphic, or remains polymorphic at a single locus (when, in the last stages of the approach to the optimum, a mutant occurs whose heterozygote brings the population to the optimum). When Gaussian stabilizing selection acts alone, there is sometimes more than one polymorphic locus, presumably because of drift near the optimum.

When frequency-dependent selection acts alone, most loci become polymorphic.

When both kinds of selection act, the proportion of polymorphic loci depends on the relative intensities of stabilization and frequency dependence. However, this relation is not very strong, and the proportion remains roughly constant over a wide range of intensities. In the five-locus model, most of the simulations end up with two or three polymorphic loci (40–60% polymorphism and 25–40% heterozygosity). In the ten-locus model, most end up with three, four or five polymorphic loci (30–50% polymorphism and 18–28% heterozygosity; see, for example, table 1). The final number of alleles at polymorphic loci varies between 2 and 5,

TABLE 1. THE FINAL ARRAY OF ALLELES AT FIVE LOCI IN EIGHT SIMULATIONS

(Under 'loci and final alleles' each of the five columns represents a locus, and the numbers in each column represent the alleles remaining at the end of the simulation. Where more than one allele is shown at a locus, the locus was in a state of polymorphism. Simulations prefixed by the same letter shared identical conditions of selection. The prefix S denotes stabilizing selection acting alone. The prefixes F, G and H denote different patterns of frequency-dependent selection ('slop' values of 0, 2 and 5 respectively) in addition to stabilizing selection. In all simulations the initial phenotypic value was 10, the optimum was 100, both A and B were 0.75 and stabilizing selection was linear. For further details, see text.)

category and generations	final phenotypic value	loci and final alleles				
		1	2	3	4	5
S1 15000	99.3	*7*	*5*	*17*	*5, 14*	*12*
S2 15000	100.0	*13*	*1*	*13*	*15*	*8*
F1 25000	100.3	*6, 9*	*1*	*16, 17, 18*	*11*	*11, 15*
F2 25000	101.2	*2, 7*	*20*	*6, 8*	*7, 11*	*12, 13*
G1 30000	99.8	*1*	*1, 6*	*18*	*7, 18*	*17*
G2 25000	98.1	*6, 17*	*3, 9*	*15*	*13*	*1*
H1 20000	99.1	*12*	*16*	*1, 17*	*1, 13*	*1, 16*
H2 25000	99.4	*4, 18*	*16*	*1, 16*	*1*	*14*

although the average is nearer 2 than 5. We cannot demonstrate that these final states are true equilibria, because no analytical methods are available for testing stability. However, in most cases the final state has persisted for more than a thousand generations before the simulation is ended. The limitations of computers, even of large ones, do not allow us to make models with more than 10 loci. The data suggest, however, that simulations with about 25 loci would give proportions of polymorphism, heterozygosities, and numbers of alleles that roughly correspond to those observed in eletrophoretic surveys of natural populations.

At an individual locus an allele may appear, invade the population, reach an apparent equilibrium that persists for several hundred generations, and then suddenly increase to fixation, decrease to loss, or move to a new apparent equilibrium. The explanation of such sudden changes is that they reflect the consequences of changes at other loci. When several genes contribute additively to a character that is under stabilizing or frequency-dependent selection, or both, the fitnesses of their genotypes are strongly epistatic. The relative selective

values of genotypes at one locus depend upon what alleles are present at the others. Each time a new allele appears and spreads, all the selective values change, and a 'genetic revolution' can occur.

When a population has reached its final state, the two kinds of selection balance each other. The selective values of all the remaining phenotypes are then approximately equal. The phenotypes nearest the optimum are predominantly heterozygotes at the polymorphic loci. Those near the extremes are predominantly homozygotes. We can do a 'thought experiment', supposing that the simulation represents a natural population of organisms, and that we remove some of these organisms to set up a population in the laboratory. In so doing we may separate them from the agents of frequency-dependent selection (predators, parasites or competitors). Only the stabilizing component of selection will then remain. Laboratory tests will show heterozygous advantage at the polymorphic loci, because the heterozygotes, on the average, are nearer the optimum. This will happen despite the fact that there was no heterozygous advantage in the 'natural' population (for indeed none was built into the simulation). The 'thought experiment' shows that apparent heterozygous advantage can be an artefact, produced by other forms of selection.

The importance of mutational order

The simulations have drawn attention to a stochastic factor that acts in addition to random genetic drift, and that is sometimes more important. It was first described by Müller (1939, 1940), but since then it has been almost completely neglected (with the honourable exception of Gillespie (1984, 1986); see below). It is the random order of mutations.

For many of our simulations, several replicates were done under identical conditions. In terms of phenotypic evolution, the results of the replicates were substantially identical. There was a rapid approach to the optimum, followed by 'stasis'. In terms of genotypic evolution, however, every replicate gave a different result. The genotypes that produced the optimal phenotype were different in each case. This happened whether or not frequency-dependent selection was present (table 1).

At first sight it seems strange that two identical populations subject to identical selection should diverge genetically, particularly when virtually all the allelic substitutions are driven by selection (the exception being the few alleles that spread by random genetic drift when a population is close to the optimum; for discussions of the selective values of alleles determining quantitative characters, see Bulmer (1980), Lynch (1984) and Barton (1986)).

The explanation for the divergence is twofold. First, when mutants first appear in a population, even advantageous alleles can be lost by drift. A different set will be lost in each population. Secondly, mutation occurs at random, and the set of alleles available to selection, and drift, will differ between the populations.

It is clear from our models that the second factor (the random order of mutations) can be more important than the first (random genetic drift). We did a series of simulations in each of which there were two pairs of populations. All four were subject to the same selective conditions. In one pair, mutation and drift were allowed to occur in the usual manner. In the other pair, however, the two populations were given identical patterns (orders) of mutation, but divergence by drift could still occur. A comparison of the pairs allowed us to estimate, by subtraction, the importance of mutational order. The simulations showed that during the response to selection, when the populations were displaced from their optimum, the effect of

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mutational order was as great or greater than that of random genetic drift. For example, we did 45 replicates with 5 loci, 32 alleles, a starting phenotype of 64, an optimum of 160, values of A and B of 0.9, linear stabilising selection, a mutation rate of 2×10^{-5}, and no linkage. After 5000 generations the median divergence, measured by Nei's Coefficient of Genetic Distance, D (Nei, 1978), was 1.26 for the pairs with fixed mutational order, and 3.19 for the pairs in which the mutational order was random. Thus the effect of mutational order was approximately 1.5 times as great as that of drift. Other simulations gave comparable figures, even when the population was started nearer the optimum (at 120).

There is one important caveat. In simulations without selection, mutational order had no obvious effect on the rate of divergence. Moreover, in simulations with selection, the influence of mutation declined after the population had come close to the optimum (i.e. during the period when the variance was becoming adjusted and the intensity of selection was decreasing). In the latter case, some of the decline in the importance of mutational order may have been due to the fact that when a population is near its optimum there are fewer alleles that can improve the fitness. None the less it was apparent that *the existence and extent of divergence due to differences in mutational order depends on the existence and strength of selection.*

It also depends, in a complicated way, on the numbers of loci and alleles, and on the sizes of their effects on the phenotype (relative to the distance from the optimum). For example, increasing the numbers of loci or alleles without any change in the average magnitudes of their effects should increase the divergence due to mutational order, but with progressively and rapidly diminishing returns. It is more difficult to predict the outcome when increments in the numbers of loci or alleles are accompanied by decrements in the magnitudes of their effects. Greater numbers of alternatives should add to the mutational divergence, but this may be counteracted by a reduction in the selective differentials between alleles. Moreover, the influence of drift should be enhanced. More work needs to be done in this area.

There is also an effect of population size. Very large populations (larger than the number of possible alleles multiplied by the reciprocal of the mutation rate) would produce most of the possible alleles in each generation, and would be more likely to show parallel or convergent evolution. With decreasing population size the rate of mutational divergence should first increase, but then decline when the population becomes very small.

In this context, we should consider what may be the true number of alternative alleles in a natural population. For the moment, let us regard a mutational step as an inherited change of an amino acid in a polypeptide chain, and its determinant as an allele, ignoring the fact that changes in different nucleotides could produce the same change of one amino acid to another. An average locus, coding for a polypeptide containing 350 amino acids, could mutate to any one of approximately 1800 different polypeptides (because each amino acid, on the average, is allowed by the genetic code to mutate in a single step to one of five or six others). If one of these mutant polypeptides appeared in a population, and became fixed in it by natural selection, a new array of approximately 1800 potential polypeptides would become available to mutation, the number varying somewhat according to codon usage. The fixation of each new allele would produce a different new array of potential alleles (Gillespie 1984). The total number of potential alleles, regardless of the number of mutational steps necessary to reach them, is of course 20^{350}, representing all the possible combinations of 20 amino acids in a sequence of 350. As well as the allelic mutations that produce changes in the amino acid sequence of a polypeptide, there will be others altering its quantity (including, perhaps,

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mutations in controlling sequences, changes in the third positions of codons, changes in introns, insertions, deletions and duplications). At the nucleotide level, an average gene, including its controlling regions and introns, might stretch for three kilobases. The total number of possible single-step nucleotide replacements would then be 9000.

The proportion of these replacements that will, at any moment, be selectively advantageous is difficult to assess. However, with so great a number of potential alleles it seems very likely indeed that more than one of them will have a selective advantage over the prevailing allele. Thus if there is a selective optimum from which the population is displaced, the route to that optimum will be dictated by whichever mutant first appears. As Gillespie (1984) pointed out, the fixation of this mutant will immediately alter the potential range of mutants available for the next selective step, and this branching process will continue.

As we have seen, when several loci affect the same character, the importance of mutational order becomes even greater. The substitution of one allele for another at any locus will cause the relative selective values of genotypes at all the other loci to change. Thus the spread of one mutant will alter the relative probabilities of fixation among all the other mutants.

In terms of genotypic evolution each of our simulations gave a different result (see table 1). Because of the argument given above, this result is not surprising. For example, with 5 loci, each having 21 alleles contributing from 0 to 20 units to the character, the number of possible homozygous genotypes that could produce an optimal value of 100 is 116601. If heterozygous genotypes are included the number is vastly greater. There is, so to speak, an adaptive landscape with more than 116000 peaks, all of equal height. The particular peak scaled by a population depends on the order in which mutation occurs. Because a real locus will have many more than 21 possible alleles, 116000 is an unrealistically modest estimate, although the number of peaks would be limited by the proportion of the potential alleles that are advantageous, which in turn depends on the distance of the population from the optimum, relative to the magnitude of the phenotypic effects at each locus. It would also be limited by the particular array of polymorphic alleles in the population at the beginning of the selection.

In some ways the system described here resembles the 'shifting balance' theory (Wright 1949). There is a great multiplicity of selective peaks, in many dimensions, so that generally a population has many paths to take. However, the 'choice' of one path rather than another does not require the population to pass through a selective trough, and therefore does not require genetic drift.

Evolutionary consequences

These findings have interesting consequences for evolutionary theory. First, if two isolated natural populations were found to live in identical or nearly identical habitats, to resemble each other at the phenotypic level, to have equal fitnesses in each others' habitats, but to differ greatly in electrophoretic genotype, it would be tempting to attribute their genotypic differences to random genetic drift. However, was can now see that this attribution might be incorrect. The divergence between the populations could have been driven entirely by selection. The effects of mutational order combined with selection can mimic those of random genetic drift.

Secondly, our findings suggest a mechanism for the origin of species. Let us suppose that two identical large populations become isolated, and then diverge because of different mutational sequences even though they are subject to very similar selective forces. What will happen if they come together and interbreed? Because the loci act additively, the F1 hybrids will have the

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same 'optimal' mean phenotype as their parents. However, in the F2 there will be a great increase in phenotypic variance, and the mean fitness of F2 hybrids will be lower than that of the parental types. Thus there will be a situation in which there could be selection for the development of barriers to mating between the two groups. Speciation could come about without any selective differences between the habitats within which the groups diverged, and without any 'bottlenecks'.

Thirdly, if mutational order is important, it gives an insight into the evolutionary role of gene flow, and a different interpretation of phenomena attributed to the Founder Principle. Mayr (1954) was led by his studies of New Guinean kingfishers (*Tanysiptera*) to stress the importance of gene flow in maintaining the 'cohesion' of the gene pool, holding together favourably coadapted associations of genes. He supposed that if a small fragment of a population became isolated, the random depletion of genetic variation among the founders could disrupt the cohesion of the gene pool and cause the new population to undergo a 'genetic revolution', so that it arrived at a new coadapted arrangement of genotypes.

The three races of *Tanysiptera galatea* inhabiting the mainland of New Guinea are barely distinguishable, despite the fact that their ranges span a distance of more than 2000 km, and cover a very wide variety of climatic conditions. However, the races that live on small islands off the coast of New Guinea are strikingly different from each other and from the mainland forms, despite the fact that the islands are less than 200 km from the mainland, and that each island occupies approximately the same climatic district as the nearest part of New Guinea.

We can offer a simpler explanation of patterns like those in the kingfishers. *The importance of gene flow is that it maintains the homogeneity of mutational order*. This homogeneity can be preserved over a large area if the flow is strong enough for an advantageous mutant appearing in one population to invade the others before different advantageous substitutions occur within them. According to this interpretation, the island races are distinct because they are cut off from gene flow, and therefore have different sequences of mutations. The physical differences are interpreted as pleiotropic manifestations of the genotypic differences, or correlated responses to the selection. Our model resembles Mayr's in that it requires epistasis, and emphasizes the importance of gene flow, but it does not demand 'bottlenecks', drift, or 'genetic revolutions'. Both models suppose that a changed genetic environment will cause different arrays of mutations to be favoured, setting in train a further series of divergent changes, at the phenotypic as well as the genotypic level.

When there is gene-flow that is not strong enough to ensure homogeneity throughout the entire range of a continuously distributed species, the range will become subdivided into a series of areas within which particular alleles are fixed (or common), separated from other such areas by steep clines. The areas for different loci need not necessarily correspond, because they may be dictated by the random occurrence of particular mutants (or indeed migrants) in particular populations. Patterns like these, termed 'area effects' (Cain & Currey 1963), have been reported in many animal species that have low mobilities.

A final matter of interest is that the computer simulations with balancing selection show changes of evolutionary rate in the phenotype that are more dramatic than those in the genotype. As we have already mentioned, the phenotype goes through a rapid shift followed by stasis. At the same time the genotype undergoes an episodic but more gradual change. This difference is due in part to different scales of measurement. When assessing genotypic divergence (for example, by Nei's Coefficient of Genetic Distance, D (Nei 1978)) a substitution

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having a large phenotypic effect is given the same weight as one having a small effect. However, this is not the whole story. Genotypic changes continue long after the phenotypic mean has approached the optimum, as a result of selection that adjusts the variance. Some of these changes involve several loci at once, because of epistasis. It was argued several years ago that epistasis can generate 'evolutionary viscosity', and thereby provide a selective explanation for the molecular clock (Clarke 1970).

A selective model of the clock, based on a great refinement of this view, has been formulated by Gillespie (1984, 1986). Mani (1984) has shown by simulation that other selective models can also explain the observed patterns of natural polymorphism and clock-like evolutionary change.

Wilson (1976), noting the relative inconstancy of estimated evolutionary rates for morphological characters and the relative constancy for molecular ones, suggested that the difference comes about because the two kinds of characters are subject to different evolutionary forces. He argued that morphological changes may predominantly come from mutations in the controlling regions of the DNA, and are more often subject to natural selection, whereas changes detected by elecrophoresis are due to mutations in the coding DNA of structural genes, and are more often influenced by random genetic drift. Because a very simple model of selection on a metrical character shows a similar discrepancy between phenotypic and genotypic rates, Wilson's dual explanation may not be necessary.

It is clear, from the arguments developed above, that two populations can converge with respect to a metrical character while diverging with respect to the genes that determine it. Of course, if they diverge with respect to the character, their genotypes will also diverge. Thus there will be no necessary connection between divergence at the phenotypic level and divergence at the genotypic level. Such patterns may help to explain the discrepancies between morphological and elecrophoretic measures of divergence found in some organisms, for example in land snails of the genus *Partula* (Johnson *et al.* 1986*a*, *b*).

Conclusions

Observations of garden birds have led, by logical steps, to some hypotheses about molecular evolution. This paper is an essay on the 'connectedness' of biology.

Our models have shown that frequency-dependent and stabilizing selection acting on metrical characters can maintain extensive polymorphism among the genes that determine these characters. They have shown that selectively-driven genotypic evolution can continue long after the phenotypic mean of a population has reached its optimum. They have drawn attention to Müller's theory of mutational divergence, and its relevance to discussions of molecular evolution. In so doing they have demonstrated a stochastic factor in evolution that is dependent for its effect on the presence of natural selection, and that in some circumstances is more important than random genetic drift. Because of its stochastic nature, mutational divergence can form the basis for a selective theory of 'molecular clocks'. The models have also offered simple explanations of 'area effects', of phenomena that have been attributed to the 'Founder Principle', and of apparent discrepancies between morphological and molecular rates of divergence. Models such as these can form a bridge between the theories of population genetics and quantitative genetics.

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