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Evolution on holey landscapes

The search for authentic ancient DNA

New tools for analysis of population genetic data

Extraordinary sex ratios



Evolution and speciation on holey adaptive landscapes

Sergey Gavrillets

Simple verbal and mathematical models have proved to be indispensable in identifying and understanding general properties of complex phenomena in physics, biology and economics. A common minimal model for discussing biological evolution and speciation considers an individual as a set of genes that has some probability of surviving to reproductive age. An individual's genes and the probability of survival are referred to as its genotype and fitness, respectively. The set of all possible genotypes is referred to as genotype space. The relationship between genotype and fitness is one of the most important factors in determining the evolutionary dynamics of populations. This relationship can be visualized using the metaphor of 'adaptive landscapes'¹, of which two versions exist². In the first interpretation, which is much more common but sometimes misleading, an adaptive landscape is a surface in a multidimensional space that represents the mean fitness of the population as a function of gamete (or allele) frequencies. A population is represented as a point on the surface. This interpretation is a derivative of a much more fundamental construction in that the adaptive landscape represents individual fitness as a function defined on the genotype space. As defined above, the genotype space is discrete and, thus, the adaptive landscape is a set of points. But for visualization purposes it is more convenient to represent the genotype space as continuous and the adaptive landscape as a continuous surface in a multidimensional space. An individual is represented as a point on this surface, and a population is represented as a cloud of points. Here I will use the latter interpretation of adaptive landscapes.

An important feature of adaptive landscapes is that the dimension, d , of the multidimensional space where an adaptive landscape is defined is enormous. For example, with n diallelic loci, $d = n + 1$ (i.e. the dimension has the order of the number of loci). We live in a three-dimensional world. Therefore it is quite natural that three-dimensional images such as mountains come to mind when one attempts to imagine a multidimensional surface. All mountain massifs are rugged. The outstanding parts of any massif are its peaks and valleys; 'ridges' are less common. A path at the same level will lead around a nearby peak and back to the starting point, and the

Sewall Wright's powerful metaphor of rugged adaptive landscapes has formed the basis for discussing evolution and speciation for more than 60 years.

However, this metaphor, with its emphasis on adaptive peaks and valleys, is to a large degree a reflection of our three-dimensional experience. Both genotypes and phenotypes of biological organisms differ in numerous characteristics, and, thus, the dimension of 'real' adaptive landscapes is much larger than three. Properties of multidimensional adaptive landscapes are very different from those of low dimension. Consequently, something that is seen as a theoretical challenge in a low-dimensional case might be a trivial problem in a multidimensional context and vice versa. In particular, the problem of how a population crosses an adaptive valley on its way from one adaptive peak to another, which Wright attempted to solve with his shifting balance theory, may be non-existent. A new framework is emerging for deepening our understanding of evolution and speciation, which provides a plausible multidimensional alternative to the conventional view of rugged adaptive landscapes.

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only way to a distant location is across valleys. Not surprisingly, it is 'rugged' adaptive landscapes¹ with adaptive peaks of different height and adaptive valleys of different depth that have received most attention within the framework of adaptive landscapes (see Fig. 1). Adaptive peaks are interpreted as different species, adaptive valleys between them are interpreted as unfit hybrids³, and adaptive evolution is considered as local 'hill climbing'⁴.

However, the metaphor of 'rugged landscape', with its emphasis on local peaks, has problems and several of its assumptions and implications can be questioned⁵⁻⁸. For instance, do different species have different fitnesses? Are small differences in fitness important in speciation? Are local peaks attainable given mutation, recombination and finite population size? Does formation of a new species always imply a (temporary) reduction in fitness? It does not look as if there are compelling reasons for a positive answer to any of these questions. Finally, accepting the metaphor of rugged adaptive landscapes immediately leads to a fundamental problem realized already by Wright himself: how can a population evolve from one local peak to another across an adaptive valley when selection opposes any changes away from the current

adaptive peak? To solve this problem Wright⁹ proposed a (verbal) shifting-balance theory. Recent formal analyses^{6,8} of different versions of the shifting-balance theory have led to the conclusion that although the mechanisms underlying this theory can, in principle, work, the conditions are very strict. Another possibility of escaping a local adaptive peak is provided by founder-effect speciation, but the generality of this scenario remains controversial^{3,10-12}.

The point here is that the metaphor of 'rugged landscape' is questionable and might even be misleading. Recently a new metaphor of 'holey adaptive landscapes' has been put forward in several independent studies as a plausible alternative to the conventional view of 'rugged adaptive landscapes'. This metaphor, which can be traced to a two-locus two-allele model proposed by Dobzhansky¹³ (see Box 1), puts special emphasis on 'ridges' of well-fit genotypes that extend throughout the genotype space. My aim here is to describe this new emerging approach to the modeling of evolution and speciation.

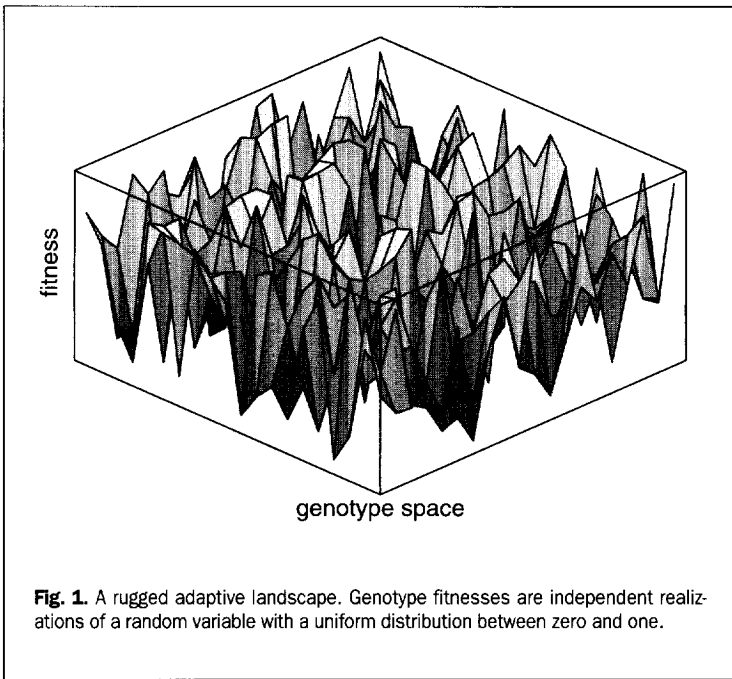
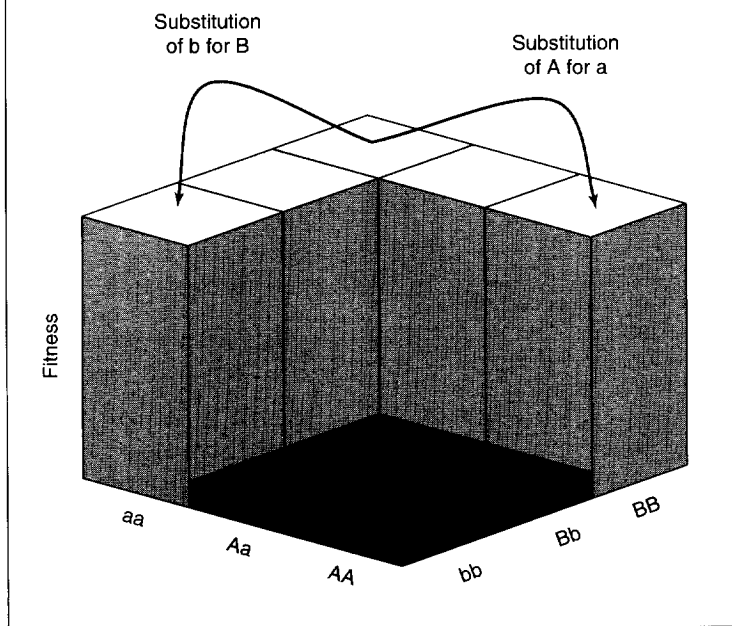


Fig. 1. A rugged adaptive landscape. Genotype fitnesses are independent realizations of a random variable with a uniform distribution between zero and one.

Box 1. Dobzhansky's model

I use the standard notation denoting alternative alleles at a locus with bold capital and lower-case letters and representing genotypes by the corresponding combinations of genes. Dobzhansky's original model¹³ considers a two-locus two-allele population initially monomorphic for a genotype, say **aaBB**. This population is broken up into two geographically isolated parts. In one part, mutation (and possibly selection) causes substitution of **A** for **a** and a local race **AABB** is formed. In the other part, mutation (and possibly selection) causes substitution of **b** for **B**, giving rise to a local race **aabb**. It is assumed that there is no reproductive isolation among genotypes **AABB**, **AaBB** and **aaBB** and among genotypes **aaBB**, **aaBb** and **aabb**, but fitness of double heterozygotes **AaBb** is small.

In this scheme, strong postzygotic reproductive isolation between races with the genotypes **AABB** and **aabb** can be achieved, even though selection acting during the evolutionary divergence is weak or absent. This model assumes that two reproductively isolated genotypes **AABB** and **aabb** are connected by a chain of well-fit genotypes **AaBB**-**aaBB**-**AaBb**. The figure below presents a Dobzhansky-type fitness landscape with fitnesses of the genotypes along the ridge set to one and fitnesses of the remaining genotypes set to one tenth. For analyses and discussions of different aspects of Dobzhansky-type population genetics models, see Refs 7, 12,23,29,35-41.



The structure of holey landscapes

To train our intuition about the large-scale properties of adaptive landscapes let us start with a simplified model⁷. Let us consider adaptive landscapes arising if genotype fitnesses are generated randomly and independently and are only equal to zero (inviable genotype) or one (viable genotype) with probabilities P and $1-P$, respectively. An appropriate image of resulting 'holey' adaptive landscapes is a multidimensional flat surface with many holes (see Fig. 2).

This model is based on three assumptions. The first assumption is that fitnesses are generated randomly. Random assignment of fitnesses is often used to get ideas about some 'general' properties of population genetics models^{14,15} and is a standard method for generating multidimensional fitness landscapes⁴. Given the current level of information about the genetic basis of adaptation¹⁶, this is a legitimate method for studying multilocus models. The second assumption is that fitnesses are generated independently and, thus, the resulting landscape is 'uncorrelated'. This assumption, which implies that even a single substitution results in an independent fitness value, is probably more difficult to justify biologically. It limits the set of genes incorporated into the model to those that are 'crucial'. Generalizing the approach to 'correlated' landscapes is one of the most important directions for future work. The final assumption that fitnesses can take only two values – zero and one – may seem bizarre. However, the model is intended for analyzing large-scale properties of fitness landscapes and genotype space. On a larger scale it may not be appropriate to assume that different species have different fitness. What is known is that there are some 'good' combinations of genes representing fit individuals and 'bad' combinations of genes representing unfit individuals (e.g. hybrids between different species). Moreover, random genetic drift, which is increasingly important in multilocus systems^{17,18}, will decrease the effect of fitness differences. Thus, the third assumption is applicable to much more general settings than it might initially appear. The probability P can be interpreted as the probability of getting a viable genotype after combining genes randomly. Accordingly, P will be considered to be small. The number of loci, n , will be large.

The main theoretical prediction of the model is that viable genotypes form 'clusters' in the genotype space. Members of a cluster can be connected by a chain of viable single-gene substitutions. Properties of these clusters, which are known as connected components, can be identified using methods from percolation theory (see Box 2). In general, there are two qualitatively different regimes: subcritical, which takes place when $P < P_c$, and supercritical, which takes place when $P > P_c$. The critical value P_c , which is known as the 'percolation threshold', depends on model details. In the case of diploid genotypes that differ in a large number, n , of loci with k alleles each, $P_c \approx 1/2[2n(k-1)]$. At the boundary of two regimes, all properties of adaptive landscapes undergo dramatic changes, a physical analogy of which is a phase transition. In the subcritical regime there are many small components, whereas in the supercritical regime there is a single 'giant' component that includes a significant part of all viable genotypes and 'percolates' through the whole genotype space^{7,19-21}. In the subcritical regime, typical members of a component can be connected by a single sequence of viable genotypes. Thus, there is a single possible 'evolutionary path'. In contrast, in the supercritical regime, typical members of the giant component are connected by many evolutionary paths.

Consider a genotype g_0 on the largest component. As we move along a chain $\{g_0, g_1, g_2, \dots\}$ of viable genotypes away from g_0 , where g_i and g_{i+1} differ in a single gene, after some i steps any offspring of g_0 and g_i will be inviable. In other words,

sooner or later genotypes g_0 and g_i will happen to be on opposite sides of a 'hole' in the fitness landscape. According to the biological species concept^{13,22}, genotypes g_0 and g_i can be considered as representing two different species. Figure 3, which gives a lower bound on the probability of speciation after j substitutions, shows that speciation is an inevitable consequence of genetic divergence on a holey adaptive landscape (cf. Ref. 23).

Let us now consider an overall number S of mutually reproductively isolated genotypes that can be put on the largest component of viable genotypes and an expected number S_j of those within j viable substitutions from a member of the largest component, say genotype g_0 . S can be interpreted as the maximum possible number of species that there can be. S_j characterizes the 'density' of different species in a region of genotype space centered at g_0 . In the subcritical regime, S has order n and S_j has order j . In the supercritical regime, S has at least order n^2 and S_j has at least order jn . Thus, in the supercritical regime both the overall number of species and their 'density' in the genotype space are at least n times higher than in the subcritical regime. Figure 4 illustrates the dependence of the maximum possible number of species on the probability of being viable P . Here the probability of being viable has been identical for all genotypes. See Refs 7 and 23 for related results on models where P depends on heterozygosity.

Rugged landscapes

The results just described allow one to get additional information about uncorrelated rugged landscapes that have been studied in a pioneering paper by Kauffman and Levin⁴ and in subsequent publications stimulated by that paper (see numerous papers on rugged landscapes at the Sante Fe Institute electronic archive at <http://www.santafe.edu/>). These fitness landscapes arise if genotypic fitness, w , is a realization of a random variable having a uniform distribution between 0 and 1 (see Fig. 1). Let us assume that there is a rugged landscape. Let us introduce two threshold values, w_1 and w_2 such that $w_2 - w_1 = P$, and construct a holey landscape in that a genotype has fitness 1 if its fitness in the corresponding rugged landscape is between w_1 and w_2 (see Fig. 5). According to the results on holey landscapes if P is above the percolation threshold, there exists a giant component of genotypes with fitnesses between w_1 and w_2 in the corresponding rugged landscape. That means that the rugged landscape has 'bands' with genotype fitnesses between w_1 and w_2 that continuously extend throughout the genotype space. If one chooses $w_2 = 1$ and $w_1 = 1 - P$, it follows that rugged landscapes have very high 'ridges' (with genotype fitnesses between $1 - P$ and 1) that continuously extend throughout the genotype space. In a similar way, if one chooses $w_2 = P$ and $w_1 = 0$, it follows that rugged landscapes have very deep 'gorges' (with genotype fitnesses between 0 and P) that also continuously extend throughout the genotype space.

The existence of chains of well-fit genotypes that connect reproductively isolated genotypes was postulated in Dobzhansky-type models (see Box 1). In contrast, the models just described show it to be inevitable under broad conditions. Given that two populations can be represented as two distinct clouds of points on a holey landscape, the existence of (biological) species will be a simple consequence of the fact that not all possible combinations of genes are viable.

The dynamics on holey landscapes

Both S and S_j values characterize the potential for speciation. To understand how speciation can happen, one should consider evolutionary dynamics on adaptive landscapes.

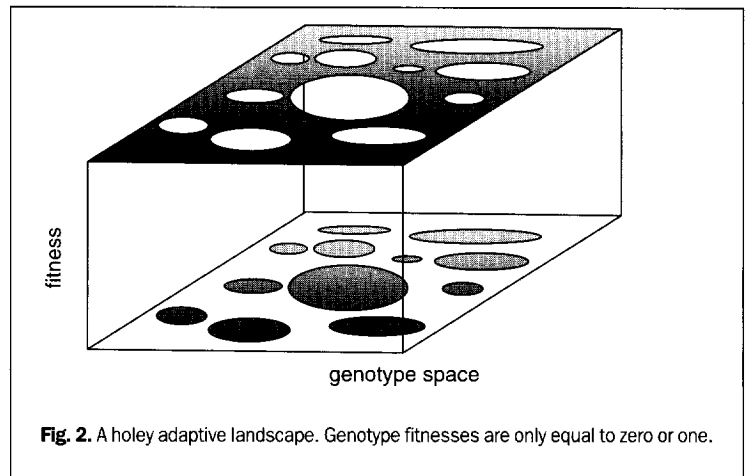


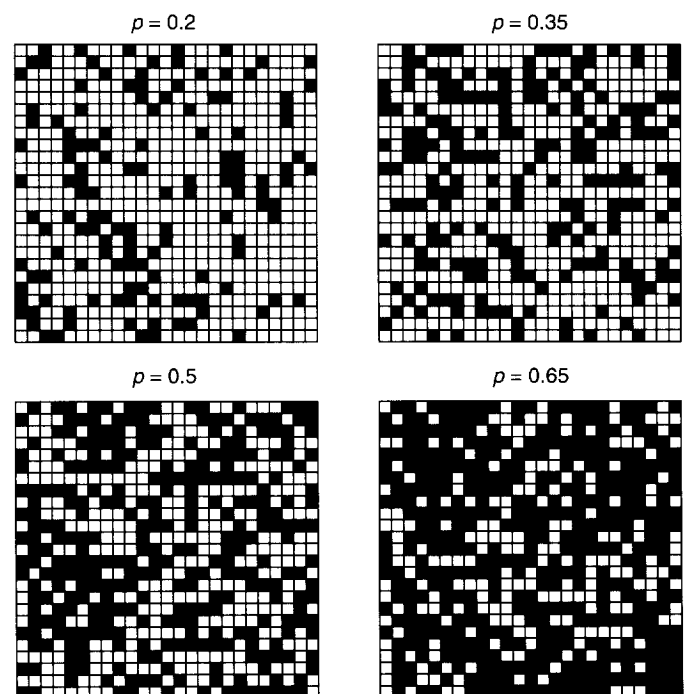
Fig. 2. A holey adaptive landscape. Genotype fitnesses are only equal to zero or one.

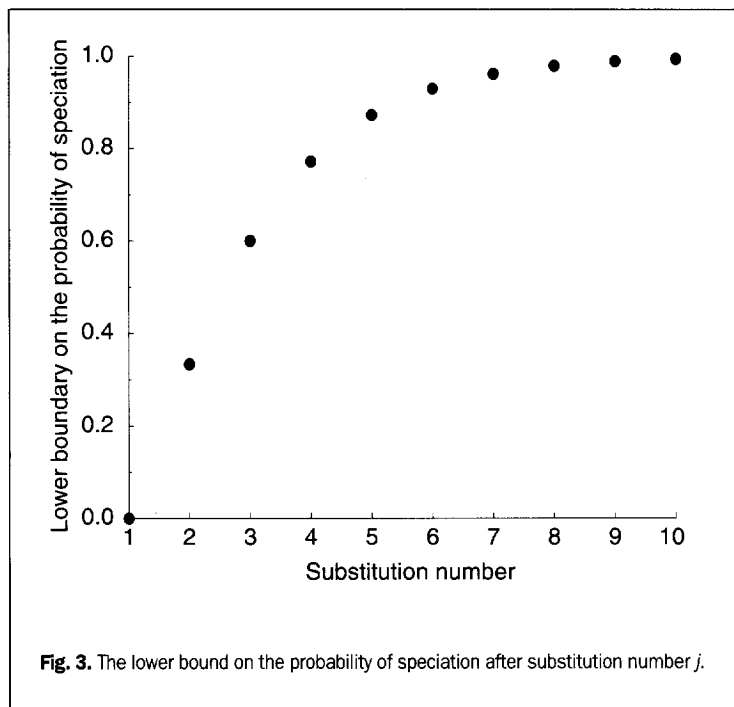
In discussing evolution on adaptive landscapes, it is useful to visualize an individual as a point in the genotype space. Accordingly, a population will be a cloud of points, and different populations (or species) will be represented by different

Box 2. Percolation

Under any form of random fitness assignment, viable genotypes will generally form clusters in the genotype space. Clusters of sites in multidimensional spaces are the subject of percolation theory⁴², whose terminology and methods I illustrate here using a simple model.

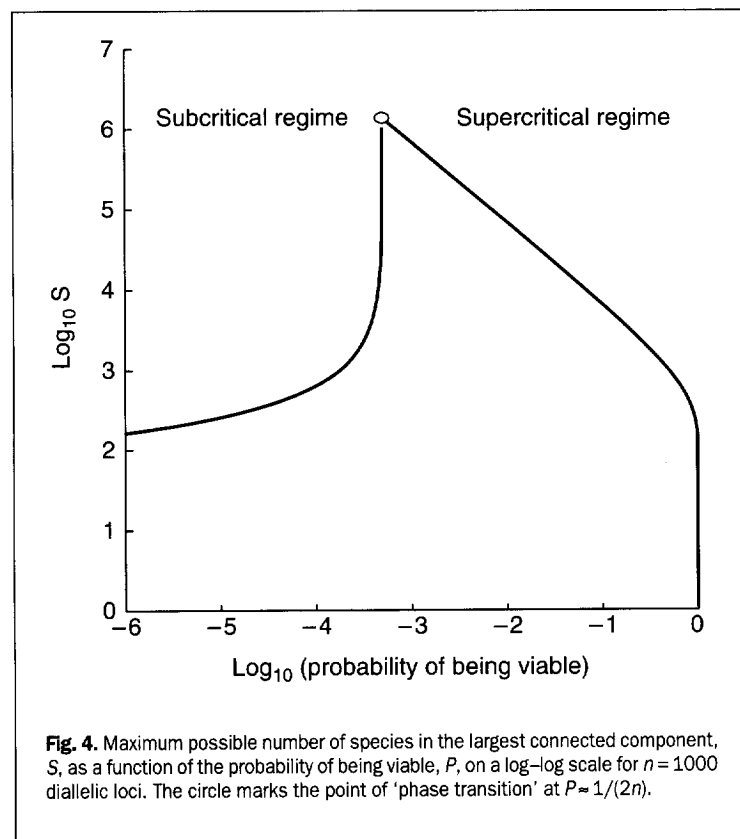
Consider a two-dimensional lattice of square sites in which sites are independently 'viable' (and painted black) or 'inviable' (and painted white) with probabilities p and $1-p$, respectively. For each site, its 'neighbors' are the four adjacent sites (above, below, on the left, and on the right). Two viable sites are said to be connected if there exists a sequence of viable sites connecting those two and subsequent sites in the sequence are neighbors. For any viable site a connected component is a set of all viable sites connected to the site under consideration. The number and the structure of connected components depend on the probability of being viable, P (see the figure below). For small values of P there are many connected components of small size. As P increases, the size of the largest connected component increases as well. As P exceeds the 'percolation threshold' $P_c \approx 0.593$, there is a giant component that 'percolates' through the whole system and includes a significant part of the viable sites. In this model describing site percolation on a two-dimensional lattice, the percolation threshold P_c has order one. The percolation threshold, however, dramatically decreases in multidimensional spaces.





clouds. Selection, mutation, recombination, random drift and other factors change both the location and the structure of these clouds. The simplest and most probable (within the present framework) scenario of biological evolution on holey landscapes is that it starts with a (set of) genotype(s) from the largest component and proceeds along this component by mutation and genetic drift. In this scenario, there is no need to cross any 'adaptive valleys'; reproductive isolation between populations evolves as an inevitable side effect of accumulating different mutations.

Consider a population on a rugged adaptive landscape. A finite population subject to mutation is likely to be found on a



fitness level determined by mutation-selection-random drift balance. Genotypes with fitnesses close to this level form a corresponding giant component (see Fig. 5). The population is prevented by selection from 'slipping' off the giant component to genotypes with lower fitness and by mutation (and recombination) from 'climbing' to genotypes with higher fitness. A population that has reached the giant component should be kept on it and further evolution should proceed in a quasi-neutral fashion according to the properties of the corresponding holey landscape. According to this scenario, microevolution and local adaptation can be viewed as the climbing of the population towards the holey landscape, whereas macroevolution and speciation can be viewed as a movement of the population along the holey landscape.

In a system with many loci, standard population genetics analyses in terms of gamete frequencies are impossible. For instance, with 10 diallelic loci there are 2^{10} different gametes. Thus, one would need to analyze more than 1000 coupled equations. Another complication follows from the fact that, even in very large populations with hundreds of thousands of individuals, each specific genotype is represented only by a small number (probably just one or zero) of copies. Thus, deterministic methods that neglect random genetic drift are very difficult to justify in multilocus evolution. Fortunately, other approaches, mainly developed in physics, can be used for studying the dynamics of multilocus systems.

Evolution of asexual populations on holey adaptive landscapes

Let there be n diallelic loci. Evolution of an asexual haploid population via mutation and random drift can be modeled as random-walk diffusion on the vertices of a hypercube (Fig. 1 in Ref. 1 presents hypercubes corresponding to $n = 2, 3, 4$ and 5). Holey adaptive landscapes can be incorporated in this model by assuming that only a proportion, P , of vertices can be accessed. Percolation theory tells us that if $P < P_c \approx 1/n$, there are many components of viable genotypes but they are all small (with order n different genotypes). In this case no significant evolutionary changes are possible.

In contrast, if $P > P_c$, there exists a giant component of accessible genotypes. 'Quasi-neutral' evolution on this giant component has been studied^{24,25}. After a sufficiently long time, the population is equally likely to be at any of the points of the component. Numerical simulations and analytical approximations have shown that the populations diverge according to the stretched exponential law^{24,25}.

Evolution of sexual populations on holey adaptive landscapes

In sexual populations, recombination and segregation introduce additional genetic load. As a consequence the population is more likely to spend more time in regions of higher frequency of fit genotypes^{26,27}. The rate of genetic divergence in this model has not been studied yet.

Evolution of asexual populations in the vicinity of a fitness peak

As was argued above, macroevolution and speciation on a rugged landscape should proceed according to properties of the corresponding holey landscape. A study²⁸ of interactions of selection, mutation and drift illustrates this claim. Woodcock and Higgs²⁸ have considered a multiplicative fitness model that implies the existence of a single adaptive peak. Using a combination of analytical approximations and numerical simulations, they have shown that after reaching a state of mutation-selection-drift equilibrium the population wanders through a band of genotypes at a certain distance below the

peak. In a rugged landscape with many local peaks, bands of genotypes surrounding each local peak will be connected in the corresponding giant component. The population is likely to remain within this component evolving in a quasi-neutral fashion.

The previous section demonstrated the plausibility of ridges of well-fit genotypes that extend through the genotype space. Models described in this section have shown that populations readily diverge along these ridges via mutation and random drift. Founder events can substantially increase the rate of evolution along the giant component¹². Genetic divergence inevitably results in reproductive isolation. No passing through adaptive valleys is necessary.

Testing the models

Mathematical models describing the structure of and evolution on holey adaptive landscapes make specific assumptions and specific predictions about properties of biological populations. These theoretical assumptions and predictions can be tested against properties of natural and laboratory populations, giving a possibility of falsifying the models. Properties of natural and laboratory populations can be used for identifying holey adaptive landscapes whereas theoretical results on holey adaptive landscapes may be useful in interpreting experiments and data, and, probably, in suggesting new experiments. Box 3 summarizes existing experimental evidence for holey adaptive landscapes.

Artificial hybridization experiments can be used to recreate a ridge of well-fit intermediate genotypes connecting two (sub-) species (provided it exists). Hybrid zones provide information about natural hybridization experiments. Some properties of the hybrid zone are indicative of selection acting on populations. The properties of hybrid zones that are maintained by a balance of migration and 'holey'-type epistatic selection can be contrasted with those formed when adaptive peaks are isolated²⁹. Under this kind of epistasis, which can be called 'rugged'-type, any deviation from a 'coadapted' combination of genes results in a (significant) reduction in fitness – there are no conditionally neutral substitutions.

A major difference between the two types of hybrid zones should be in the distribution and fitnesses of genotypes in the center of the hybrid zone. Let the fitness of F_1 hybrids be small, that is, reproductive isolation is strong. At 'rugged'-type hybrid zones besides the high fitness parental forms one should observe mainly low-fitness F_1 hybrids. In contrast, at 'holey'-type hybrid zones besides the parental forms one should observe other high-fitness genotypes different from F_1 hybrids. At 'rugged'-zone hybrid zones one expects concordant clines in neutral allele frequencies. In contrast, at 'holey'-type hybrid zones, clines in the frequencies of neutral genes linked to selected loci are expected to be disjointed.

A common null model in interpreting patterns of morphological changes and speciation observed in the fossil record is random diffusion in morphospace³⁰. An implicit assumption of this model is that all possible directions for evolution are equally probable. An explicit assumption of the metaphor of holey adaptive landscape is that evolution proceeds mostly along 'permissible' directions represented by ridges of well-fit genotypes. Random diffusion on a hypercube with holes represents an alternative model for macroevolutionary changes. One can use this model for generating theoretical predictions which can be contrasted with existing paleontological data.

Future work

Standard approaches to the modeling of speciation have been deficient in several ways. Usually a small number (one or two) of loci or quantitative traits are considered, whereas,

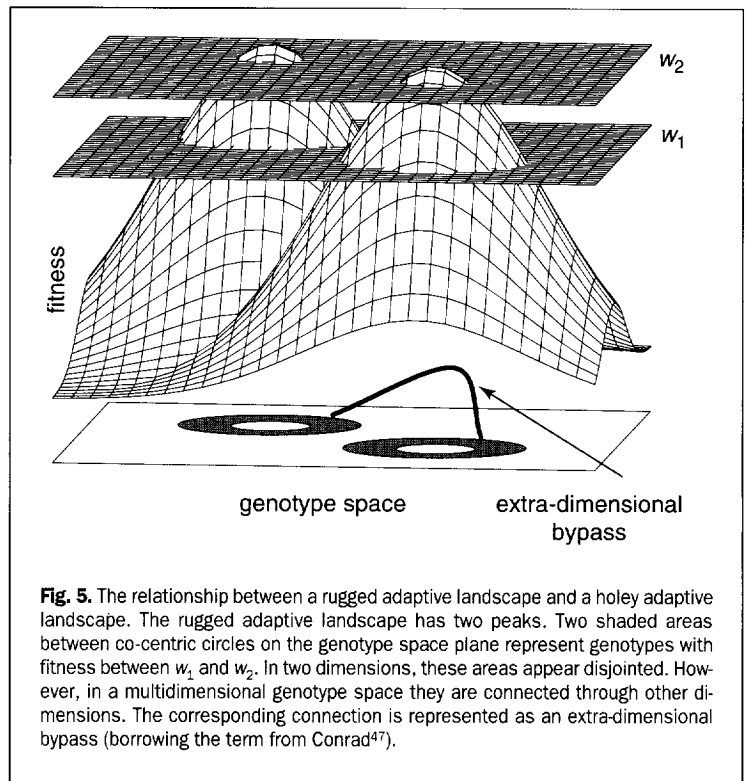


Fig. 5. The relationship between a rugged adaptive landscape and a holey adaptive landscape. The rugged adaptive landscape has two peaks. Two shaded areas between co-centric circles on the genotype space plane represent genotypes with fitness between w_1 and w_2 . In two dimensions, these areas appear disjointed. However, in a multidimensional genotype space they are connected through other dimensions. The corresponding connection is represented as an extra-dimensional bypass (borrowing the term from Conrad⁴⁷).

in general, species are different with respect to many loci and traits. Selection is assumed to be weak, whereas in natural populations hybrids are usually not produced at all or have strongly reduced fitness which implies that selection is very strong. Population size is considered to be very large, whereas in nature genetic drift should be ubiquitous. Only a very limited number of selection regimes mostly reflecting the dominant paradigm of 'rugged adaptive landscapes' have been studied, whereas the form of selection is largely unknown and the utility and generality of the metaphor of 'rugged adaptive landscapes' is questionable.

Box 3. Experimental evidence for holey adaptive landscapes

Experimental evidence for holey adaptive landscapes has been accumulating. A few recent references include studies of male-sterility mutations (discussed in Refs 39,40), tumorigenesis in hybrids between *Xiphophorus maculatus* and *X. helleri* and the abnormal abdomen syndrome of *D. mercatorum* (both discussed in Ref. 41), hybrid inviability in plants and hybrid inviability or sterility in *D. pseudoobscura* (both discussed in Ref. 23), different 'synthetic lethals' in *Drosophila* and plants (discussed in Ref. 43), chromosomal evolution of mammalian taxa, where different centric fusions with one homologous and one nonhomologous arm have been fixed in different populations (discussed in Ref. 44), and the divergence of warning color in the burnet moth, *Zygaena ephialtes* (discussed in Ref. 8).

Epistatic interactions revealed in these studies imply the existence of a chain of well-fit genotypes connecting two genotypes that are reproductively isolated to some degree. Both the results of a large-scale selection experiment⁴⁵, where artificial selection dramatically changed a population without reducing its fitness, and the structure of a grasshopper hybrid zone (discussed in Ref. 8) manifest underlying holey adaptive landscapes as well. With some reservations, 'ring species' can be considered as the best manifestation of holey adaptive landscapes. Ring species are circularly arranged polytypic taxa with gradual transitions between adjacent components but abrupt changes and reproductive isolation where the terminal races come into contact. Nine cases of ring species were described in Ref. 22 and more than a dozen additional cases were documented in Ref. 46. Recent analyses of RNA sequences and secondary structures^{20,21,32} suggest that 'holey adaptive landscapes' may be common in sequence space as well. These studies predict the existence of connected networks of RNA sequences with identical secondary structures; frequent structures are distributed almost randomly and percolate through sequence space. Finally, the existence of fit intermediates between radically different morphologies has been observed in the fossil record.

The approach described here allows us to relax some of these limitations. Theoretical studies of evolution on holey adaptive landscapes may be crucial both for our understanding of micro- and macroevolution and for directing experimental work. By explicitly considering many loci, finite populations, and strong selection, these studies would extend earlier work to more realistic situations. The framework described here, using methods of population genetics for analyzing speciation, is a step towards bridging the gap between microevolutionary and macroevolutionary modeling. At the same time, concentrating on 'quasi-neutral' or 'conditionally neutral' genetic changes as the basis of speciation, this framework is a step towards bridging the gap between neutralist and adaptationist approaches. Considering genetic divergence and reproductive isolation simultaneously, theoretical models may clarify the meaning of species and the relationships between different species concepts³¹. Holey adaptive landscapes may be important in microevolution as well, for they can be 'used' by a population to escape a low-fitness local maximum³². Thus, understanding evolution on holey adaptive landscapes may increase our understanding of local adaptation and microevolution.

Obviously, the approach is not free of limitations and some holes can be shot in the argument presented. Among the most significant are that it includes no ecological factors, considers only fixed adaptive landscapes, and, thus, allows no coevolution. Only 'uncorrelated' holey landscapes have been systematically studied. Possibilities for genetic divergence and speciation on holey adaptive landscapes introduced by recombination^{33,34} have so far not been explored. These limitations must be removed in future work.

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