Contents

This is a very rough draft!!!

> "Perhaps our ultimate understanding of scientific topics is measured in terms of our ability to generate metaphoric pictures of what is going on. Maybe understanding *is* coming with metaphoric pictures" (Bak, P. "How Nature Works" 1996).

Biological evolution is an extremely complex process influenced by a large number of genetical, ecological, environmental, developmental and other factors. To understand a very complex phenomenon, it is very helpful to have a simple metaphor[1] for this phenomenon. During the last seventy years Wright's (1932) metaphor of "adaptive landscapes" has been a standard tool for visualizing biological evolution and speciation. This metaphor is widely considered as one of his most important contributions to evolutionary biology (e.g., Provine 1986). At the same time, Wright's metaphor has also become a subject of some controversy. As articulated by Provine (1986), there are actually two rather different versions of adaptive landscapes which Wright himself used interchangeably creating a confusion. This confusion was not resolved by Provine's (1986) otherwise wonderful book. Here I will attempt to clarify this issue.

1 Adaptive landscapes: basic ideas and definitions

A fundamental idea of evolutionary biology is that different individuals in a population have different genes and that these genetic differences lead to differences in fitness. In other words, genetic variation results in selection (variation-selection-inheritance). The relationship between genotype and fitness is of a fundamental importance. The metaphor of adaptive landscapes provides a simple way to visualize this relationship. Implicitly it also emphasizes the importance of specific mechanisms and patterns in evolutionary dynamics. Before formally defining adaptive landscapes it is useful to start with a simple population genetic model.

1.1 Working example: one-locus two-allele model of viability selection

Let us consider a large randomly mating diploid population with non-overlapping generations. We concentrate on a single diallelic locus controlling fitness. Using standard notation, **A** and **a** will stand for the alternative alleles at the locus under consideration, and the three diploid genotypes will be **AA, Aa** and **aa**. To complete the model one needs to specify genotype fitnesses w_{AA}, w_{Aa} and w_{aa}. Here, by a genotype's fitness we will mean the genotype's viability (that is the probabilities to survive to the age of reproduction). Figure 1a visualizes the relationship between genotype and fitness in this model for a specific choice of fitness values. This Figure depicts two unequal "peaks" (at genotypes **AA** and **aa**) separated by a "valley" (at genotype **Aa**).

If the population size is very large and constant, the genetic structure of the population can be described in terms of the frequencies x, y and z of genotypes **AA, Aa** and **aa**, respectively. Under Hardy-Weinberg equilibrium, genotype frequencies can be expressed in terms of allele frequencies. If p and $1-p$ are the frequencies of alleles **A** and **a**, then the genotype frequencies are $x = p^2, y = 2p(1-p)$ and $z = (1-p)^2$. Now the genetic structure of the population can be described by a single variable p. With regard to fitness, the population can be characterized by the mean fitness

$$\overline{w}(p) = w_{AA}\ p^2 + w_{Aa}\ 2p(1-p) + w_{aa}\ (1-p)^2 \tag{1}$$

which depends on allele frequency p. Figure 1b visualizes the (quadratic) relationship between the mean fitness of the population $\overline{w}(p)$ and allele frequency p using the same numerical values of parameters as

[1]**Metaphor** – 1 : a figure of speech in which a word or phrase literally denoting one kind of object or idea is used in place of another to suggest a likeness or analogy between them; 2 : an object, activity, or idea treated as a metaphor (*Merriam-Webster's Collegiate Dictionary*, http://www.m-w.com/).

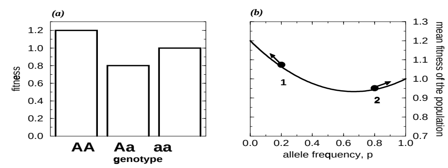

Figure 1: Visualization of the relationships between genotype and fitness in a one-locus two-allele model with $w_{AA} = 1.2, w_{Aa} = 1.0, w_{aa} = 1.1$. (a) Genotype fitnesses. (b) The mean fitness of the population $\overline{w}$ as a function of allele frequency p.

in Figure 1a. Function $\overline{w}(p)$ has two unequal "peaks" (at $p = 0$ and $p = 1$) separated by a "valley" (at $p = 2/3$).

In the model under consideration, the function $\overline{w}(p)$ is very important because it controls the change in allele frequency, Δp, between two subsequent generations. Specifically, as shown by Wright (1935),

$$\Delta p = \frac{p(1-p)}{2} \, \frac{d \ln \overline{w}(p)}{dp}. \tag{2}$$

In a polymorphic population (that is in a population with $p \neq 0, p \neq 1$), the factor in front of the derivative in the right-hand side of the last equation is always positive ($\frac{p(1-p)}{2\overline{w}(p)} > 0$). Thus, if for a current value of p function $\overline{w}(p)$ is decreasing (implying that the derivative $\frac{d\overline{w}(p)}{dp}$ is negative; e.g. point 1 in Figure 1b), the allele frequency p will decrease ($\Delta p < 0$) approaching zero asymptotically. If for a current value of p function $\overline{w}(p)$ is increasing (implying that the derivative $\frac{d\overline{w}(p)}{dp}$ is positive; e.g. point 2 in Figure 1b), the allele frequency p will increase ($\Delta p > 0$) approaching one asymptotically. In this model, depending on the initial state the population will evolve towards fixing one allele on another. At either fixation state, the average fitness of the population is maximized. In general, in one-locus models with constant viability selection the population evolves to a state where the mean fitness reaches a local maximum - the fact reflected in Fisher's fundamental theorem of natural selection (e.g. Nagylaki 1992).

Figures 1a and 1b provide two alternative ways to visualize evolutionary dynamics. Using Figure 1a, one can think of an individual as a "point" sitting on top of the bar corresponding to the individual's genotype (**AA, Aa** or **aa**). The height of the bar specifies individual fitness. A population will be a group of "points" sitting at possibly different bars. As time progresses, the distribution of the points will change concentrating more and more on one of the two homozygotes (**AA** or **aa**). Using Figure 1b, one thinks of a population as a point on the curve $\overline{w} = \overline{w}(p)$. The point's abscissa characterizes the genetic structure of population (described by the allele frequency p). The point's ordinate specifies the mean fitness of the population. As time progresses, the point moves uphill ending up on one of the two peaks (at $p = 0$ or $p = 1$).

Of the two relationships visualized in Figure 1a and 1b, the first, that is the relationship between genotype and fitness, is more simple and fundamental. It does not invoke any assumptions about the forces governing the evolutionary dynamics. The second relationship, that is the one between the allele frequency p and the mean fitness $\overline{w}(p)$, is a derivative of the first one in the sense that if one knows how individual fitness depends on genotype, it is straightforward to find how the mean fitness depends on genotype (or allele) frequencies. The second construction implicitly invokes the assumption of fitness maximization. In the example considered above this assumption is perfectly justified. However, in other cases it might be not. A common features of both relationships is the existence of multiple (here, two) local “peaks” with (possibly) different heights. Note that in Figure 1a both the independent and dependent variables take discontinuous discrete values. In contrast, in Figure 1b both the independent and dependent variables are continuous.

There are two different versions of *adaptive landscapes*. In the first, **adaptive landscape is a relationship between genotype and fitness** (as depicted in Figure 1a). In the second, **adaptive landscape is a relationship between variables characterizing the genetic structure of a population and its mean fitness** (as depicted in Figure 1b). The one-locus two-allele model just considered is very simple which allows one an easy and transparent way to visualize the both types of adaptive landscapes. The following section illustrates the problems encountered in visualizing these relationships when there are more alleles and/or loci.

1.1.1 Appendix: Derivation of Wright's equation $\Delta p = \frac{p(1-p)}{2}\frac{d\ln\overline{w}(p)}{dp}$

We consider a one-locus two-allele population with alleles **A** and **a**. There are three possible genotypes **AA, Aa** and **aa**. Let p and q and x, y and z be the corresponding allele and genotype frequencies. Immediately after reproduction, the genotype frequencies among offspring are in Hardy-Weinberg proportions: $x = p^2, y = 2pq, z = q^2$. We assume that genotypes are different with respect to *viability* defined as the probabilities of survival to the age of reproduction. Let w_{AA}, w_{Aa} and w_{aa} be the corresponding viabilities. The genotype frequencies after (viability) selection are $x_s = cw_{AA}x, y_s = cw_{Aa}y, z_s = cw_{aa}z$ where c is a normalizing coefficient necessary to satisfy the condition $x_s + y_s + z_s = 1$. This coefficient is $1/\overline{w}$ where

$$\overline{w} = w_{AA}x + w_{Aa}y + w_{aa}z = w_{AA}p^2 + w_{Aa}2pq + w_{aa}q^2 = w_{AA}p^2 + w_{Aa}2p(1-p) + w_{aa}(1-p)^2,$$

is the mean fitness of the population. The allele frequency after selection is

$$p_s = x_s + y_s/2 = \frac{w_{AA}x + w_{Aa}y/2}{\overline{w}} = \frac{w_{AA}p^2 + w_{Aa}pq}{\overline{w}} = \frac{w_A}{\overline{w}}\ p,$$

where $w_A = w_{AA}p + w_{Aa}q$ is the *induced* fitnesses of allele **A**. Because reproduction does not change the allele frequencies, the allele frequencies in the offspring, p', will be equal to p_s. Thus, we have shown that under viability selection the dynamics of allele frequency are described by a recurrence equation

$$p' = \frac{w_A}{\overline{w}}\ p. \tag{3}$$

We can also consider the change in allele frequency between two subsequent generations, $\Delta p = p' - p$. One can show that the following equalities are true

$$\Delta p = \frac{w_A - \overline{w}}{\overline{w}} p \tag{4a}$$

$$= pq\frac{w_{Aa} - w_{aa} + (w_{AA} - 2w_{Aa} + w_{aa})p}{\overline{w}} \tag{4b}$$

$$= pq\frac{\frac{1}{2}\ \frac{d\overline{w}}{dp}}{\overline{w}} \tag{4c}$$

because $d\overline{w}/dp = 2[w_{Aa} - w_{aa} + (w_{AA} - 2w_{Aa} + w_{aa})p]$.

1.2 Adaptive landscape as fitness of gene combinations

In the original Wright's (1932) formulation adaptive landscape represents fitness of gene combinations. To construct an adaptive landscape, first one specifies a *genotype space*, and then assigns *fitness* to each gene combination in the genotype space. **Genotype space is defined as a set of all possible genotypes**[2]. For example, in the model considered above, the genotype space consisted of three genotypes **AA, Aa** and **aa** which can be arranged along a line according to the number (0, 1 or 2) of alleles **a** (or **A**) present (see Figure 1a). The visualization of the resulting adaptive landscape requires using two dimensions: one

[2]Wright himself referred to a “field of possible gene combinations”.

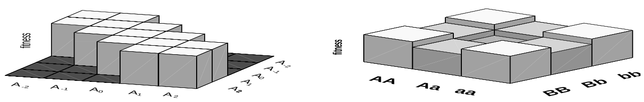

Figure 2: (a) Adaptive landscape in Nei et al. (1983) one-locus multi-allele model of post-mating reproductive isolation. It is assumed that allele $\mathbf{A}_i$ can mutate only to alleles $\mathbf{A}_{i+1}$ and $\mathbf{A}_{i-1}$ and that any two alleles separated by more than one "mutational steps" are incompatible (in the sense that the corresponding genotype has zero fitness). (b) Adaptive landscape in a two-locus two-allele model with $w_{11} = w_{13} = w_{31} = w_{33} = 1, w_{12} = w_{21} = w_{23} = w_{32} = 0.8, w_{22} = 0.6$

for the genotype space and one for fitness. With more alleles and/or loci the situation becomes more complicated. In some simple cases the genotype space can be adequately described by using only two dimensions thus giving a possibility to describe an adaptive landscape in three dimensions. For example, this is possible a one-locus multi-allele model with stepwise mutation (Nei et al. 1983) (see Figure 2a). Also, in many cases the adaptive landscapes corresponding to two-locus two-allele models of viability selection with alleles **A** and **a** at the first locus and alleles **B** and **b** at the second locus can be adequately described by 3×3 fitness matrix

	BB	**Bb**	**bb**
AA	w_{11}	w_{12}	w_{13}
Aa	w_{21}	w_{22}	w_{23}
aa	w_{31}	w_{32}	w_{33}

,

where w_{11} is fitness of genotype **AABB**, w_{12} is fitness of genotype **AABb** etc. An adaptive landscape in such a model is visualized in Figure 2b.

However, in general three dimensions are not sufficient for describing the adaptive landscapes. The genotype space corresponding to L haploid diallelic loci consists of 2^L different genotypes. This genotype space can be represented by the vertices of a L-dimensional hypercube. Figure 3 redrawn from Wright's (1932) original figure shows the hypercubes corresponding to $L = 2, 3, 4$ and 5. In this figure, the genotypes differing in a single gene ("one-step neighbors") are connected by an edge, and different genotypes are arranged along the x-axis according to the number of mutational steps (genetic distance) to a reference genotype represented by a chain of low-case letters. With more than two alleles per locus, the genotype space can be represented by the vertices of a *generalized hypercube* or an *undirected graph* (see an example given in Figure 4). The *dimensionality* of the genotype space is defined as the number of one-step neighbors each genotype has. If the loci are diallelic ($k = 2$), the dimensionality of the genotype space is equal to the number of genes L (see Figure 3). In general, with k alleles at each of L genes, there are L^k different genotypes, and the dimensionality of the corresponding genotype space is $L(k-1)$. The dimensionality of the genotype space corresponding to the two-locus three-allele system depicted in Figure 4 is $2 \times (3 - 1) = 4$. Wright (1932) discussed an example of "a species with 1000 loci each represented by 10 allellomorphs." In this case, the genotype space has $1000 \times (10 - 1) = 9000$ dimensions and consists of 10^{1000} genotypes.

Note that in the one-locus two-allele model represented in Figure 1a we manage to use only one dimension for the genotype space rather than two because of the implicit assumption that heterozygotes **Aa** and **aA** have identical fitnesses. In biological terms this assumption means the absence of *pater-*

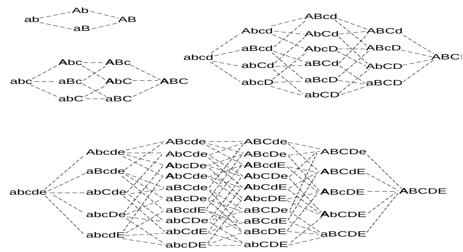

Figure 3: Genotype space in L-locus two-allele haploid systems with $L = 2, 3, 4$ and 5. Genotypes differing in a single gene ("one-step neighbors") are connected by an edge, and different genotypes are arranged along the x-axis according to the number of mutational steps (genetic distance) to a reference genotype represented by a chain of low-case letters. Redrawn from Wright (1932).

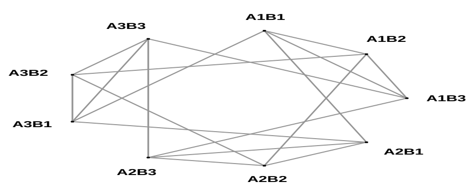

Figure 4: Genotype space in a two-locus three-allele haploid system. Genotypes differing in a single gene ("one-step neighbors") are connected by an edge.

nal/maternal effects. In the one-locus five-allele model represented in Figure 2a two dimensions (rather than $2 \times (5-1) = 8$) are sufficient because of the symmetry assumption and an explicit assumption that alleles can be arranged in a "natural" order according to the step-wise patterns of mutations. In the two-locus two-allele model represented in Figure 2b we used only two dimensions for the genotype space instead of four ($= 4 \times (2-1)$) because of the implicit assumption that both paternal/maternal effects and *cis- and trans- effects* are absent. The latter means that fitnesses of genotypes formed by gametes **AB** and **aB** and genotypes formed by gametes **aB** and **AB** are identical. However, in general, the genotype space has a huge number of dimensions. Plus one needs an extra dimension for fitness. In contrast, we are limited by two or three dimensions for visualization purposes.

1.3 Adaptive landscape as the mean fitness of populations

The mean fitness of the population depends on its genetic structure. In general, the number of variables necessary to describe the genetic structure of a population equals the number of different genotypes minus one. (Because the sum of all genotype frequencies is one, the frequency of one of them can be found if the frequencies of all other genotypes are known.) This number gives the dimensionality of the corresponding population state space. The genetic structure of a randomly mating population under constant viability selection with no maternal/paternal and cis/trans effects can be described by a set of

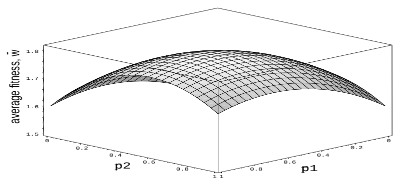

Figure 5: Adaptive landscape in a two-locus two-allele model with additive fitnesses. The contributions of **AA, Aa** and **aa** to fitness are 0.9, 1.0 and 0.8, respectively. The contributions of **BB, Bb** and **bb** to fitness are 0.8, 1.0 and 0.7, respectively. p_1 and p_2 are the frequencies of alleles **A** and **B**, respectively.

variables the number of which is equal to the number of possible haplotypes minus one. For example, in a one-locus two allele model considered at the beginning of this chapter there are two different haplotypes (alleles). Thus, one needs a single variable (e.g. the frequency of an allele) to describe a population. In standard two-locus two-allele models there are four different haplotypes. The frequencies of any three haplotypes are sufficient to describe the genetic structure of such a population. Alternatively, one can use two allele frequencies and linkage disequilibrium. Thus, in general one needs four dimensions (three for the population state plus one for fitness) to visualize the adaptive landscape in these models. However, with additive fitnesses the mean fitness does not depend on linkage disequilibrium (e.g. Nagylaki 1992) and, thus, three dimensions will be sufficient (see Figure 5). With L diallelic loci there are 2^L gamete. Thus, the dimensionality of the corresponding adaptive landscape will be 2^L. Assuming that fitnesses are additive reduces the dimensionality to L. The same reduction can be achieved by assuming the absence of linkage disequilibrium so that the population state is adequately described by L allele frequencies.

This second version of adaptive landscapes is very useful for modeling optimization. Also, it can be appropriate if the number of loci is very small (one or two) or if linkage disequilibrium is absent. However for our purposes, this version of adaptive landscapes will not be particularly useful. First, it is well known that the mean fitness of the population does not necessarily increase. Second, from a pragmatic point of view, the process of speciation where a population splits into two different species is impossible to describe in a framework where a population is the smallest unit. Finer resolution is necessary for describing the splitting of populations. Third, there are problems with using this version in a multilocus context. In this version, the population state is described in term of genotype frequencies. However, even with a small number of loci the number of possible genotypes becomes much bigger than the population size. For example, with 20 diallelic loci there can be $2^{20} \approx 10^6$ different haploid genotypes. This means that most genotype frequencies will be equal to zero. In this case, the population description by listing genotype frequencies reduces to describing the population state by listing all genotypes present which is exactly what is done in the first version of adaptive landscapes. In what follows we will mostly use the first version of adaptive landscapes.

[If one knows fitnesses of gene combinations, it is straightforward to find the average fitness of the population. If one knows the average fitness of a population, one cannot say anything about individual fitnesses. The dimensionality of the adaptive landscape in the second version is enormous making its usage less clear. In the second version, the structure of the landscape can be affected by the population size. Changing variances can change the structure. First version concentrates on individuals; second - on populations.]

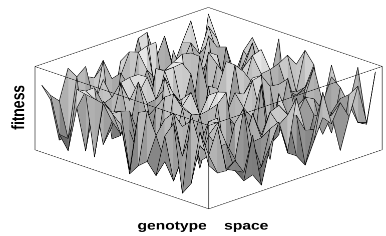

Figure 6: A rugged adaptive landscape

2 Classical types of adaptive landscapes

The relationships between genotype and fitness are, in general, unknown. Only recently direct studies of specific fitness landscapes such as RNA fitness landscapes (refs) started to appear. Moreover, because of the huge disperancy between the number of dimensions necessary to define an adaptive landscape and the number of dimensions available for us, adaptive landscapes cannot be graphically described in their entirety even if they were known. Also, in the most general version, both the genotype space and adaptive landscape are discrete sets rather than continuous surfaces. However, it is much more convenient to represent them as continuous. All this results in that to visualize an adaptive landscape, one necessarily has to simplify and emphasize only specific features thought to be most important while neglecting many other features.

2.1 Wright's rugged adaptive landscapes

Wright vision of a typical adaptive landscape was that of a "rugged" surface having many isolated local "adaptive peaks" of different height separated by "adaptive valleys" of different depth (see Figure 6). Adaptive peaks represent well-fit combinations of genes (coadapted gene complexes). Wright reasoned that interactions of the effects of different loci on fitness coming from pleiotropy and epistasis will make the existence of multiple adaptive peaks unavoidable. Different adaptive peaks can be viewed as alternative solutions to the problem of survival which all biological organisms face. Adaptive peaks that are sufficiently far away from each other in the genotype space may be thought of as corresponding to different (potential) species. Adaptive valleys between peaks represent low-fitness combinations of genes. These include both genotypes with deleterious genes (e.g., resulting from deleterious mutations) and genotypes with incompatible genes (e.g. resulting from hybridization).

Adaptive peaks are important because of the expectation that natural selection will "drive" biological populations towards them. This expectation has been supported by numerous population genetic models demonstrating, as a rather general rule, increase in fitness as a result of evolution. Within the framework of adaptive landscapes adaptive evolution is considered as local "hill climbing." The next section considers the properties of hill climbing on a specific rugged landscape following the work of Kauffman and Levin (1987) and Kauffman (1993).

2.1.1 Hill climbing on an uncorrelated rugged landscape

Let there be L haploid diallelic loci. Each genotype can be represented as a binary (that is with elements 0 and 1) sequences of length L. The corresponding genotype space can be represented by a binary

L-dimensional hypercube (see Fig. 3). Assume that the fitness value of each genotype is drawn at random from a uniform distribution. This results in an uncorrelated random rugged landscape. [Here, "uncorrelated" means that similar genotypes do not necessarily have similar fitnesses.] We will consider random walks on such landscapes. We assume that at each step the walk samples one-step neighbors at random and moves to the first fitter genotype encounter. [Two genotypes are one-step neighbors if they differ at a single gene.] A move to a one-step neighbor corresponds to a mutation getting fixed in a specific locus. Modeling biological evolution using such a random walk makes several simplifications. Specifically, it is assumed that (i) there is no genetic variation in the population (which can be a reasonable approximation if the number of mutants per generation is small), (ii) deleterious mutations are never fixed, (ii) advantageous mutations are never lost, and (iii) the probability of fixation does not depend on the effect of mutation.

For several questions considered above, we will use the fitness ranks of genotypes (counted from the list fit genotype with rank 1 to the fittest genotype with rank $T = 2^K$) rather than actual fitnesses. For simplicity we assume that there are to "tie values." The properties of adaptive walks via the first fitter one-step neighbor sampled by the mutation process starting with a randomly chosen genotype were studied in (Kauffman and Levin 1987, Kauffman 1993). The following is a sample of their results.

- The number of local maxima is very large

  $$M = 2^L/(L+1). \tag{5}$$

  For example, with $L = 100$, $M = 2^{100}/101 \approx 1.26 \times 10^{28}$, with $L = 1000$, $M \approx 10^{299}$.

  [The probability that a genotype is a local maximum is the probability that it has higher fitness rank than any of its L one-step neighbors: $1/(L+1)$. Because the total number of L-locus two-allele genotypes is 2^L, the expected number of local maxima is given by formula (5).]

- The expected fraction of fitter one-step neighbors dwindles by 1/2 on each improvement step.

  [Assume that the adaptive walk begins from the lowest ranked genotype. All its L neighbors are fitter with fitness ranks spread between 2 and $T = 2^L$. The walk samples neighbors at random and moves to the first one fitter one encounter. One average, the fitness rank of the first fitter neighbor lies halfway to the top. When the process moves to that neighbor, only half of its one-step neighbors are still fitter. On average, each successful step jumps half the remaining distance to the top rank; hence at each step the expected number of fitter one-step neighbors dwindles by 1/2.]

- Walks to local optima are short and vary as a logarithmic function of L. The average number of steps till reaching a local maximum is $r = \log_2(L-1)$. For example, with $L = 100$, $r \approx 6.63$, with $L = 1000$, $r \approx 9.96$.

  [Starting from the lowest fitness genotype, the expected relative fitness rank at step r is $x/T = (2^r - 1)/2^r$, which is equal to $1/2, 3/4, 7/8, \dots$ for $r = 1, 2, 3, \dots$, respectively. The probability that the newly encountered genotype is a local maximum is $(x/T)^{L-1}$. Note that the exponent is $L-1$ rather than L because we do not count the "ancestral" genotype. Thus, the probability P_r that an adaptive walk continues for r steps without encountering a local maximum is

  $$P_r = \Pi_{i=0}^{r} \left[1 - \left(\frac{2^i - 1}{2^i} \right)^{L-1} \right]$$

  The value of r at which $P_r \approx 1/2$ yields an estimate of expected walk lengths. This value is approximately $r = \log_2(L-1)$.]

- The expected time to reach an optimum (including the waiting time till a fitter neighbor is found) is proportional to the dimensionality of the space.

  [Since on average the adaptive walk steps halfway to the top rank et each improvement step, the expected waiting time to find a fitter variant *doubles* after each improvement step. The first improvement step requires one moment, the second on average requires two moments, the third requires four moments etc. Because the expected number of steps to reach a local optimum is $\log_2(L-1)$, the expected waiting time is

$$t_{opt} = \sum_{i=0}^{\log_2(L-1)} 2^l \approx L - 1.$$

- The ratio of accepted to tried mutations scales as $\ln k/k$.

  [This follows from the fact that the length of a walk is the number of accepted mutations and the time of the walk is the number of tried mutations.]

- Any walker can climb to only a small fraction of the local maxima. For example, with $L = 100$ the upper boundary on the number of local maxima accessible from the least fit genotype is 4.4×10^5, and with $L = 1000$ the boundary is 2.8×10^{14}.

  [L one-step neighbors can be reached after the first step, $L/2$ other neighbors can be reached after the second step, approximately $L/4$ one-step neighbors can be reached after the third step and so on. Thus the number of different paths is approximately

$$B = \frac{L}{1} \times \frac{L}{2} \times \frac{L}{4} \times \cdots \times \frac{L}{L} = \frac{L^{\log_2(L)}}{2^{\log_2(L)(\log_2(L)+1)/2}} = L^{(\log_2(L)-1)/2},$$

  where it is assumed that there are $\log_2(L)$ steps. Assuming that different "paths" lead to different maxima, the above number gives an upper boundary on the number of local optima accessible from the lowest ranked entity.]

- A small fraction of the walkers can climb to any one maximum.

  [Let us find the number of genotypes that can climb to the global maximum. This is also the number of genotypes one can *descend* to via one-step *less fit* neighbors. The fittest genotype could reach L less fit neighbors. Each of those has $L/2$ still less fit neighbors, and each of those has on average $L/4$ less fit neighbors and so on. Thus, the overall number of genotypes after $\log_2(L)$ steps is

$$L + L\,\frac{L}{2} + L\,\frac{L}{2}\,\frac{L}{4} + \cdots + L\,\frac{L}{2}\,\frac{L}{4}\cdots\frac{L}{L} = \sum_{i=1}^{\log_2 L} L^i 2^{-i(i+1)/2}.$$

  For example with $L = 128$ the above number is 5.5×10^6, with $L = 1024$, the number is 9.3×10^{14}.]

- Conjecture: As L increases, the heights of accessible peaks fall towards the mean fitness - "The Complexity Catastrophe". This has been shown for Kauffman's NK-model.

After a finite number of steps, which in general is rather small, no direction for adaptive evolution is available anymore (there are no advantageous mutations). As soon as the population reaches a neighborhood of a local adaptive peak, any "movement" of individuals away from the adaptive peak is prevented by selection. It is important to realize that the peak the population has reached does not necessarily have the highest fitness. On the contrary, it is much more plausible that the peak has an intermediate height and (much) higher fitnesses are possible. Without additional forces populations (and species) will stop evolving after some transient time (see above).

This conclusion leads to two important questions. The first question is how fitness be can increased further. The second questions is how new species can be produced. Both processes are impossible without a way for a population to keep changing genetically after reaching a local peak. There are two possible solutions. First, additional factors acting against selection and overcoming it at least occasionally can drive the population across an adaptive valley. The factor that has received most attention in this regard is *random genetic drift* by which one usually means stochastic fluctuations in the genetic composition of a population due to accidents of sampling in gametogenesis, Wright 1977, p.444). Second, temporal changes in the adaptive landscape itself can result in continuous genetic changes driven by selection if the population continuously climbs uphill chasing an optimum that continuously moves. The next section considers the possibility of stochastic transitions across valleys of maladaptation.

2.1.2 The rate of stochastic transitions between peaks: one-locus two-allele case

The probability of fixation. Let $u(p)$ be the ultimate probability of fixation of allele **A** given that its initial frequency is p. Let $M_{\delta p}$ and $V_{\delta p}$ be the mean and the variance of the change in gene frequency, p, per generation. Then, $u(p)$ satisfies to a linear homogeneous second order ordinary differential equation

$$M_{\delta p} u'(p) + \frac{1}{2} V_{\delta p} u''(p) = 0 \tag{6}$$

with boundary conditions $u(0) = 0, u(1) = 1$ (e.g., Kimura 1964). The solution can be explicitly found by standard methods. This solution is

$$u(p) = \frac{\int_0^p G(x)dx}{\int_0^1 G(x)dx}, \tag{7a}$$

where

$$G(x) = e^{-\int \frac{2M_{\delta x}}{V_{\delta x}} dx}. \tag{7b}$$

Fisher-Wright binomial scheme for random genetic drift. With finite N, the allele frequency change will have a stochastic component coming from the inherent stochasticity in the way that alleles present in adults are sampled to pass to offspring. This stochasticity is commonly referred to as "random genetic drift." There are different ways to describe random genetic drift mathematically. The most common way is based on the so-called Fisher-Wright (or Wright-Fisher) binomial scheme. In this scheme, the value of the allele frequency, $p_{offspring}$, in offspring is treated as randomly drawn from the binomial distribution $Bin(p_{adult}, 2N)$ with parameters p_{adult} and $2N$ where the former is the frequency of allele **A** among reproducing adults and the latter is the overall number of alleles in the (diploid) population. The underlying assumption is that each adult produces a very large (effectively infinite) number of gametes of which $2N$ are randomly sampled to form the next generation. Under the Fisher-Wright scheme the expected change in p between two subsequent generation is equal to zero, $M_{\delta p} = 0$, whereas the expected variance in the change in p is equal to

$$V_{\delta p} = \frac{p(1-p)}{2N}. \tag{8}$$

Additive allele. Let the fitnesses of genotypes **aa**,**Aa** and **AA** be $1, 1+s$ and $1+2s$, respectively. The expected change in allele frequency $M_{\delta p}$ can be found using Wright's equation (2) assuming weak selection ($s << 1$):

$$M_{\delta p} = sp(1-p).$$

The expected variance in the change in p is given by equation (8). Substituting these values into the general expression (7) one finds that the probability of fixation is

$$u(p) = \frac{1 - e^{-2Nsp}}{1 - e^{-2Ns}}.$$

If there is a single copy of the mutant allele initially ($p = 1/(2N)$),

$$u(1/(2N)) = \frac{1 - e^{-2s}}{1 - e^{-2Ns}}.$$

If s is positive and small (that is allele **A** is weakly advantageous) but Ns is large (that is the population size is large), $u \approx 2s$, that is the fixation probability is approximately twice the selective advantage. In large populations, selection will overwhelm drift once the advantageous allele is at all common. But only a very small proportion of advantageous mutations have a chance to become common. For a deleterious

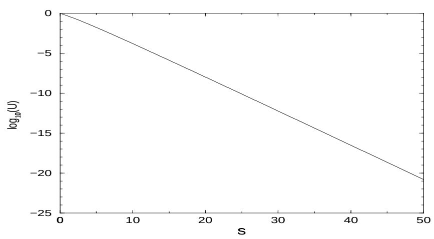

Figure 7: Rate of stochastic transitions in the underdominance model (see equation 11)

allele ($s < 0$), $u \approx 2|s|/(e^{2N|s|} - 1)$. In small populations, the fixation of deleterious alleles can occur with a non-negligible probability.

Fixation of an underdominant mutation (Lande 1979). Let us consider a one-locus two-allele diploid system with genotypes **AA, Aa** and **aa** having fitnesses (viabilities) $1, 1-s$ and 1, respectively where parameter $s \geq 0$. The adaptive landscape corresponding to this model is similar to that in Figure 1 with the difference that the two peaks have the same height (normalized to be equal to one). Assume that the population size is N.

Assuming weak selection ($s << 1$), the expected change in the frequency p of allele **A** is

$$M_{\delta p} = spq(p-q), \tag{9}$$

where q is the frequency of allele **a** ($q = 1-p$). Assume that initially all organisms are homozygotes **AA** and consider the fate of a single allele **a** introduced in the population by mutation. The initial frequency of allele **a** is $1/(2N)$. Most likely this allele will be lost but there is a small probability u that it will be fixed in the population (that is its frequency will become one). The latter event will represent a *peak shift* that is a transition from on adaptive peak to another across a valley of maladaptation. The integrals in equation (7) can be found exactly resulting in the probability of fixation

$$u(1/(2N)) = \frac{1}{2}\left(1 - \frac{erf\left[\sqrt{S}(1-\frac{1}{N})\right]}{erf\left[\sqrt{S}\right]}\right), \tag{10}$$

where $S = Ns$ and $erf(x)$ is the error function ($erf(x) = (2/\pi)\int_0^x exp(-y^2)dy$). Expanding in a Taylor series under the assumption that $1/N << 1$ results in

$$u(1/(2N)) = \frac{e^{-S}\sqrt{4S/\pi}}{erf(\sqrt{S})}\ \frac{1}{2N} \equiv U\ \frac{1}{2N}. \tag{11}$$

Note that because the probability of fixation on a neutral allele is $1/(2N)$, factor U characterizes the rate of fixation of underdominant alleles relative to that of neutral alleles. For example, if $Ns = 5$ then $U \sim 0.017$, if $Ns = 10$ then $U \sim 10^{-4}$ and if $Ns = 20$ then $U \sim 10^{-8}$. One is forced to conclude that even for moderately large populations stochastic transitions across even shallow valleys are very unlikely.

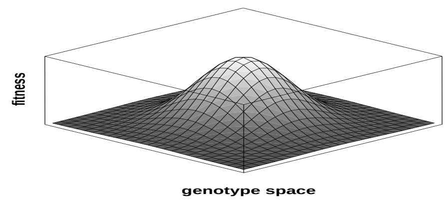

Figure 8: A single-peak adaptive landscape

2.2 Fisher's single-peak adaptive landscapes

Fisher (see Provine, 1986, pp. 274-275; Ridley, 1993, pp. 206-207) suggested that as the number of dimensions in an adaptive landscape increases, local peaks in lower dimensions will tend to become saddle points in higher dimensions. In this case, according to Fisher, natural selection will be able to move the population to the global peak without any need for genetic drift or other factors. A typical adaptive landscape implied by Fisher's views has a single peak (see Figure 8). However, recent work has shown that Fisher's criticism is not warranted: the peaks that transform to saddle points are well outnumbered by new local peaks brought by increasing dimensionality of genotype space (Kauffman and Levin 1987). This means that a typical adaptive landscape is "filled" with local peaks, and finding the global peak by selection only is, in general, impossible. However, the single-peak view may still be useful for modeling biological evolution in a neighborhood of a local adaptive peak (see below).

Single-peak landscapes arise in two classical models of multilocus selection: additive and multiplicative. In the *additive fitness regime*, the fitness, w, of an organism is found by summing up the contributions, w_i, of L individual loci:

$$w = w_1 + w_2 + \cdots + w_L.$$

The additive model may be a reasonable approximation if contributions of individual loci to fitness (or another trait under consideration) are small. Table 1 gives an example of additive fitnesses in the two-locus two-allele case ($L = 2$). Here, the entry in the i-th row and j-th columns shows the fitness of a genotype that has the specified genes in the first and second loci.

Table 1: Additive fitnesses (viabilities) in the two-locus two-allele case.

	BB	**Bb**	**bb**
AA	$a_1 + b_1$	$a_1 + b_2$	$a_1 + b_3$
Aa	$a_2 + b_1$	$a_2 + b_2$	$a_2 + b_3$
aa	$a_3 + b_1$	$a_3 + b_2$	$a_3 + b_3$

In the *multiplicative fitness regime*, the fitness, w, of an organism is found by multiplying the contributions, w_i, of individual loci:

$$w = w_1 \times w_2 \times \cdots \times w_L.$$

The multiplicative model may be a reasonable approximation if the individual loci contribute to fitness (or another trait under consideration) at different time moments. Table 2 gives an example of multiplicative

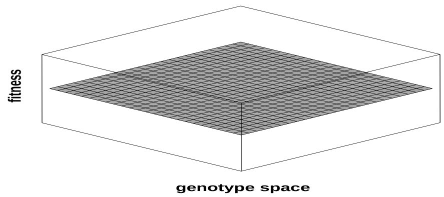

Figure 9: A flat adaptive landscape

fitnesses in the two-locus two-allele case.

Table 2: Multiplicative fitnesses (viabilities) in the two-locus two-allele case

	BB	**Bb**	**bb**
AA	a_1b_1	a_1b_2	a_1b_3
Aa	a_2b_1	a_2b_2	a_2b_3
aa	a_3b_1	a_3b_2	a_3b_3

In both the additive and multiplicative models, there is a single peak which is both local and global. For example, in Table 1 this is the genotype with fitness $max(a_i) + max(b_i)$ whereas in Table 2 this is the genotype with fitness $max(a_i) \times max(b_i)$, where $max(a_i)$ is the largest of the three value a_1, a_2 and a_3 and $max(b_i)$ is the largest of the three value b_1, b_2 and b_3.

2.3 Kimura's flat adaptive landscapes

The major claim of the neutral theory of molecular evolution (e.g., Kimura 1983) is that most evolutionary changes at the molecular level are neutral (that is do not result in changes in fitness). A typical adaptive landscape implied by this view is flat (see Figure 9). There is extensive theoretical literature on the evolutionary dynamics by random drift of selectively neutral mutations (e.g., refs). The next section summarizes some of the theoretical results that will be relevant here.

2.3.1 Evolution on flat landscapes

Random walk on a L-dimensional hypercube. Assume that an organism (or a species) is represented by a binary sequence of length L. Assume that time is discrete. At each time moment there is a (small) probability μ that an element of the sequence flips (mutation). Let d_t be the "distance" to the initial state (that is the number of elements that differ between the current and initial sequences) at time t. This distance is expected to change according to

$$d_{t+1} = d_t + v\left(1 \times \frac{L - d_t}{L} - 1 \times \frac{d_t}{L}\right) = (1 - 2\mu)d_t + L\mu,$$

where $v = L\mu$ is the overall probability of change in a unit of time (assuming that v is small, $v = L\mu << 1$). An approximate solution to the above equation can be written as

$$d_t \approx \frac{L}{2}(1 - e^{-2\mu t}).$$

This shows that d_t asymptotically approaches $L/2$; the characteristic approach time is $\ln(2)/(2\mu)$. In a similar way, one can show that the distance between two independent walkers asymptotically approaches $L/2$ with the characteristic approach time $\ln(2)/(4\mu)$.

Coalescence. Consider a finite diploid population of constant size N. We will use the Fisher-Wright binomial scheme for describing the effects of random genetic drift. In this scheme, the probability p_i that an allele leaves behind i offspring is a binomial with success probability equal to $1/N$. Let us consider k alleles. The probability x_k that they all have different "parents" is

$$x_k = (1 - \frac{1}{2N})(1 - \frac{2}{2N}) \dots (1 - \frac{k-1}{2N}) \approx 1 - \frac{k(k-1)}{4N}.$$

Thus, the probability that these k individuals have k different ancestors t generations ago and $k-1$ ancestor $t+1$ generations ago (that is the probability of a *coalescence* in generation $t+1$) is

$$x_k^t(1 - x_k) \approx \frac{k(k-1)}{4N} exp \left[\frac{k(k-1)}{4N} \ t \right].$$

This is the probability of a *coalescence* in generation $t+1$. The distribution above is geometric with probability of success $k(k-1)/(4N)$. The average time until a coalescence is the inverse of the probability of success, $E(T_k) = 4N/(k(k-1))$. Thus, any two alleles ($k = 2$) can be traced back to a common ancestor approximately $2N$ generations ago.

The rate of fixation of new alleles. If there are no selective differences between $2N$ alleles in a population, each of them has the same probability $1/2N$ of being eventually fixed (that is being represented by $2N$ copies). Let μ be the probability of mutation per generation. There are $2N\mu$ mutations on average each generations, $2N\mu \times 1/(2N)$ of which will be fixed. Thus the average number of fixed mutations per generation is equal to the mutation rate μ. The time between two substitutions follows the exponential distribution with the mean $1/\mu$ and the variance $1/\mu^2$.

Genetic distances. During the time to coalescence of any two individuals (equal to approximately $2N$ generations), each lineage accumulated approximately $2N\mu$ mutations. Thus, the expected genetic distance between a pair of individuals is $4N\mu$ (assuming that each mutation is unique which is true if L is very large).

2.3.2 Clade diversification on a morphological hypercube (Gavrilets 1999)

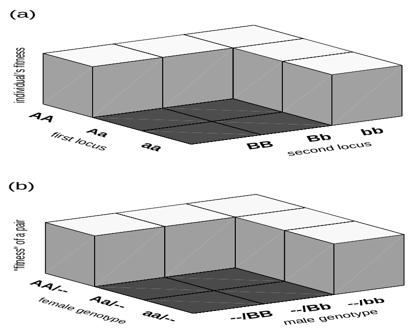

Figure 10: Adaptive landscapes for mating pairs. (a) Adaptive landscape in a one-locus two-allele multiplicative fertility model. There are three genotypes **AA**, **Aa** and **aa**. The corresponding male and female fertilities are $f_1 = 3, f_2 = 1, f_3 = 2$ and $m_1 = 3, m_2 = 2, m_3 = 1$. (b) Adaptive landscape for the probabilities of mating in no-choice tests involving *Drosophila silvestris* (DS), *Drosophila heteroneura* (DH), and their F_1 hybrids (H) (data from Gavrilets and Boake 1998, Table 1).

3 Adaptive landscapes for mating pairs

In the discussions of adaptive landscapes, fitness is traditionally interpreted as a characteristic of an individual. In most cases, it is viability that is the probability to survive to the age of reproduction. However, in many situations it is more appropriate to consider fitness (or a fitness component) as a characteristic of a mating pair of individuals. For example, fertility (that is the average number of offspring) often depends on whether maternal and paternal genes match. Another component of fitness playing extremely important role in discussions of sexual selection is the probability of mating between a male and a female given they have encountered each other. This probability can often depend on the degree of matching between the male's genes (or traits) and female preferences. The concept of adaptive landscapes can be applied to these situations by appropriately redefining the genotype space and fitness. Now the genotype space (the set of all possible combinations of genes) is defined for combinations of genes each consisting of a male genotype and a female genotype.

For example, in a classical model of multiplicative fertility selection (Bodmer 1965) the fertility of a mating is the product of the fertility effects in each sex: $F_{ij} = m_i f_j$ where f_i and m_j are fertility effects of male genotype i and female genotype j, respectively. Figure (18a) shows an example of an adaptive landscape arising in a one-locus two-allele version of this model. In Gavrilets and Boake's (1998) model of sexual selection, premating reproductive isolation is defined in terms of a 3x3 matrix of the probabilities of mating. Figure (18b) shows an adaptive landscape for mating probabilities using the data on percent mating in no-choice tests involving *Drosophila silvestris*, *Drosophila heteroneura*, and their F_1 hybrids (Gavrilets and Boake 1998, Table 1). Thus, both fertility selection and sexual selection can be treated within the conceptual framework of adaptive landscapes.

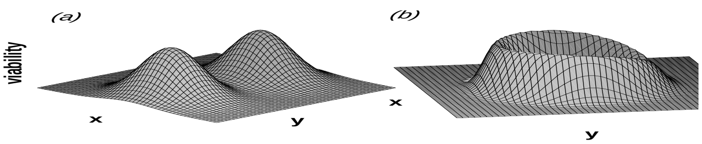

Figure 11: Adaptive landscapes with two quantitative characters. (a) A landscape with two separate peaks. (b) A landscape with a ridge of well-fit phenotypes.

4 Adaptive landscapes for quantitative characters

In the quantitative genetics framework, individuals are characterized by continuously varying quantitative traits rather than by sequences of genes. Adaptive landscapes for quantitative characters can be defined in two ways similar to those for discrete genes (Simpson 1953; Lande 1976).

In the first version, adaptive landscape is a relationship between a set of quantitative characters and fitness. Here, the role of the genotype space is played by the *phenotype space* that is the set of all possible phenotypes. The dimensionality of the phenotype space is equal to the number n of quantitative characters considered. In this version, an adaptive landscape defines fitnesses of trait combinations. With quantitative characters adaptive landscapes are continuous surfaces rather than sets of distinct points. Figure (21a) gives an example of an adaptive landscape with two peaks isolated by a valley. Figure (21b) shows an adaptive landscape with a ridge of high fitness values. These examples are from Gavrilets and Hastings (1996) paper studying the effects of genetic architecture on the plausibility of founder effect speciation.

In the second version, an adaptive landscape defines the average fitness $\overline{w}$ of a population as a function of its population genetic structure. The later is usually described in terms of the moments of the distribution of the quantitative traits in the population. The dimensionality of the population state space is equal to the number of phenotypic moments affecting the average fitness. For example, let fitness $w(x)$ be approximated as a quadratic function of a trait value, x:

$$w(x) = 1 - sx^2$$

with $s > 0$ being a parameter characterizing the strength of selection. Such a fitness function is often used to modeling stabilizing selection. Then the mean fitness of the population,

$$\overline{w} = 1 - s(\overline{x}^2 + P),$$

depends on both the average trait value $\overline{x}$ and phenotypic variance P. In this case, an adaptive landscape can be described in three dimensions (see Figure 12). Note that in theoretical quantitative genetics it is customary to assume that only average trait values change whereas variances and other moments are constant. In some situations this assumption can be justified if selection is weak and the time interval considered is relatively short. In this case, the changes in the phenotypic distribution can be adequately described by the changes in the average trait values, and the dimensionality of the population state space is equal to the number of traits considered.

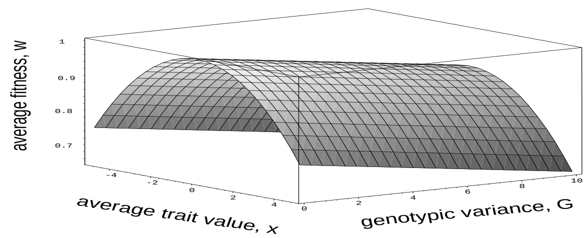

Figure 12: Average fitness of the population, $\overline{w}$, as a function of the mean trait value, $\overline{x}$, and the phenotypic variance, P, for the case of quadratic stabilizing selection, $w = 1 - sx^2$. Notice that the average fitnesses decreases with the phenotypic variance.

The average fitness of the population considered in the second version of adaptive landscapes controls the change in the mean trait value. Under simplifying conditions (ref), this change is given by an analog of Wright's equation (2)

$$\Delta\overline{x} = P\frac{\partial \ln \overline{w}}{\partial \overline{x}}, \tag{12}$$

where $\overline{w}$ is the mean fitness and P is the variance of x in the population (Lande 1976). If the phenotypic variance G is (approximately) constant the population evolves in a gradient-type fashion by approaching a local peak in $\overline{w}$. This is the situation when the second version of adaptive landscapes is especially useful.

Typically, what one means by fitness in quantitative genetic models is viability that is the probability of survival to the age of reproduction. However, the notion of adaptive landscapes can be applied to other types of fitness components. For example, a crucial component of most sexual selection models operating in terms of quantitative characters is a "preference function" Ψ controlling the probability of mating between females and males with specific phenotypes. For example, in Lande's (1981) classical model of absolute preferences,

$$\Psi = exp(-(x-y)^2/(2\nu^2)),$$

where x and y are a female's and a male's trait values, and ν is a parameter measuring mating tolerance. Preference functions can be interpreted as fitness function of potential mating pairs. Figure (13) describes an adaptive landscape arising in Lande's model of absolute preferences. In this model, most possible mating pairs x and y have low "fitness" and a small proportion of mating pairs that have high "fitness" (which are mating pairs with $x \approx y$) form a continuous network in the phenotype space. In Lande's (1981) model, random genetic drift can drive the divergence of different populations along a ridge of "well-fit" pairs of quantitative traits leading to allopatric speciation.

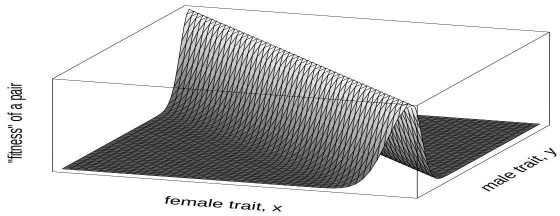

Figure 13: Adaptive landscape for mating pairs in Lande's (1981) model of absolute preferences.

4.1 Derivation of Lande's equation $\Delta\overline{x} = P\frac{\partial \ln \overline{w}}{\partial \overline{x}}$

4.1.1 Robertson-Price formula $\Delta\overline{\psi} = \frac{cov(\psi,w)}{\overline{w}}$

If $p(z)$ is the phenotypic distribution before selection, then the phenotypic distribution after selection is $p_s(z) = w(z)p(z)/\overline{w}$. Let $\psi = \psi(z)$ be a function of z. The mean value of ψ before selection is

$$\overline{\psi} = \int \psi(z)p(z)dz.$$

After selection

$$\overline{\psi}_s = \int \psi(z)p_s(z)dz = \int \psi(z)\frac{p(z)w(z)}{\overline{w}}dz.$$

The change in $\overline{\psi}$ as a result of selection is

$$\Delta\overline{\psi} \equiv \overline{\psi}_s - \overline{\psi} = \int \psi(z)\frac{p(z)w(z)}{\overline{w}}dz - \overline{\psi} = \frac{\int[\psi(z)w(z)]p(z)dz - \overline{\psi}\overline{w}}{\overline{w}} = \frac{\overline{\psi w} - \overline{\psi}\overline{w}}{\overline{w}}.$$

Thus,

$$\Delta\overline{\psi} = \frac{cov(\psi, w)}{\overline{w}}, \tag{13}$$

where $cov(a, b)$ is the covariance of a and b. This is the Robertson-Price formula. Note that no specific assumptions about the distributions and selection regimes have been made so far.

For example, if $\psi = z$, then

$$\Delta\overline{z} = \frac{cov(z, w)}{\overline{w}}. \tag{14}$$

If $\psi = z^2$, then

$$\Delta\overline{z^2} = \frac{cov(z^2, w)}{\overline{w}}. \tag{15}$$

If $\psi = \overline{w}$, then

$$\Delta\overline{w} = \frac{cov(w, w)}{\overline{w}} = \frac{var(w)}{\overline{w}} \tag{16}$$

that is the change in the average fitness is proportional to the variance in fitness. The Robertson-Price formula predicts the change in a specific population characteristic as a result of within-generation selection. Under some additional assumptions it can be used to describe the changes between generations. For example, if the trait z is additive, then recombination and segregation will not change its mean value. Thus, equation (14) describes the change in the mean trait value between two subsequent generations.

4.1.2 Lande's formula: weak selection approximation

Lande derived his formula assuming that all relevant distributions are normal. This assumption is not easy to justify. Also, the mean fitness of the population can be found easily only in some special cases. Here, we consider an alternative method of the derivation of equations analogous to (12) based on less restrictive assumptions.

We start with the Robertson-Price formula

$$\Delta\overline{z} = \frac{cov(z,w)}{\overline{w}}. \tag{17}$$

Expanding $w = w(z)$ in a Taylor series at $z = \overline{z}$, one gets

$$w(z) = w(\overline{z}) + \frac{dw}{dz}(z-\overline{z}) + \frac{1}{2}\,\frac{d^2w}{dz^2}(z-\overline{z})^2 + \dots \tag{18}$$

Using the covariance properties, we find that

$$\begin{aligned}
cov(z, w(z)) =& cov(z-\overline{z}, w(z)) \\
=& cov(z-\overline{z}, w(\overline{z}) + \frac{dw}{dz}(z-\overline{z}) + \frac{1}{2}\,\frac{d^2w}{dz^2}(z-\overline{z})^2 + \dots) \\
=& 0 + \frac{dw}{dz}cov(z-\overline{z}, z-\overline{z}) + \frac{1}{2}\,\frac{d^2w}{dz^2}cov(z-\overline{z}, (z-\overline{z})^2 + \dots \\
=& P\frac{dw}{dz} + \frac{1}{2}\,\frac{d^2w}{dz^2}\mu_3 + \dots,
\end{aligned}$$

where $\mu_3 = \int (z-\overline{z})^3 p(z)dz$ is the third moment of the distribution of z (which measures asymmetry of $p(z)$) and all derivatives are evaluated at $z = \overline{z}$.

Computing the expectation of both sides of (18), one can see that

$$\overline{w} = w(\overline{z}) + \frac{dw}{dz}\overline{(z-\overline{z})} + \frac{1}{2}\,\frac{d^2w}{dz^2}\overline{(z-\overline{z})^2} + \dots = w(\overline{z}) + \frac{1}{2}P\frac{d^2w}{dz^2} + \dots$$

Thus,

$$\Delta\overline{z} = \frac{P\frac{dw}{dz} + \frac{1}{2}\,\frac{d^2w}{dz^2}\mu_3 + \dots}{w(\overline{z}) + \frac{1}{2}P\frac{d^2w}{dz^2} + \dots}$$

which can be approximated by

$$\Delta\overline{z} = P\,\frac{d\ln w}{dz}, \tag{19}$$

where the derivative is evaluated at $z = \overline{z}$. Note that to apply (19) one needs to know the derivative of the individual fitness rather than the mean fitness of the population. The approximation is good is

$$P\frac{d^2w}{dz^2} << w(\overline{z}),\ \mu_3\frac{d^2w}{dz^2} << P\frac{dw}{dz}.$$

The former condition is satisfied if differences between fitnesses are small (weak selection). The latter condition is satisfied if differences between selection gradients, dw/dz, are small (weak non-linearity in selection; if $w(z)$ is linear, all derivatives higher than the first will be zero). Note that equation (19) can be used even if individual fitness depends on the state of the population (that is with frequency dependent fitness, e.g. $w = w(z,\overline{z})$).

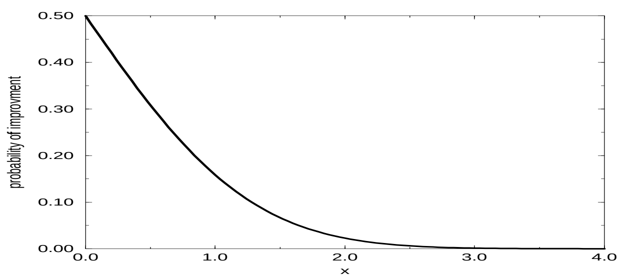

Figure 14: Probability of improvement in Fisher's (1930) model

4.2 Evolution on a single-peak landscape in Fisher's geometric model

Fisher (1930) model. Assume that each organism is characterized by n continuous variables. Let there be a single optimum phenotype (placed at the origin 0) and let fitness monotonically decrease with increasing the (Euclidean) distance from the optimum. First, let us consider a case of just two traits ($n = 2$) (see Figure ?). Let $d/2$ be the distance from the current state A to the optimum O. Any random mutation (that is any displacement in the phenotype space having random direction) is advantageous if it moves the organism inside the circle and is disadvantageous if it moves the organism outside the circle. Let r be the mutation size (that is the distance between A and mutant phenotype A') and $P(r)$ be the probability that mutation is advantageous. Note that as $r \to 0$, $P \approx 1/2$, and that for $r > d$, $P(r) = 0$. As found by Fisher, with large n (≥ 9) the probability $P(r)$ can be approximated as

$$P(r) = \frac{1}{\sqrt{2\pi}} \int_x^\infty e^{-t^2/2} dt = 1 - \Phi(x), \tag{20}$$

where $x = r\sqrt{n}/d$ is the normalized distance to the optimum, and $\Phi(x)$ is the cumulative distribution function of a standard normal distribution. Using this result (see Figure 14), Fisher argued that small mutations are the most important in adaptive evolution. Also note the higher dimensionality n, the less likely a favorable mutation is to occur.

Kimura's (1983) correction. Highly advantageous mutations have larger probability of being fixed than weakly advantageous mutations. For example, the probability of fixation of a single mutant with selective advantage s in a diploid population of size N assuming additivity is

$$u = \frac{1 - exp(-2s)}{1 - exp(-4Ns)} \approx 2s$$

and is linear with s (Kimura 1964). Kimura argued that the rate of adaptive substitutions k of mutations of normalized size x is

$$k(x) \sim 2x(1 - \Phi(x)). \tag{21}$$

The graph of $k(x)$ (see Figure 15) has a maximum at an intermediate value of x suggesting that mutations of intermediate effects are the most important in adaptation.

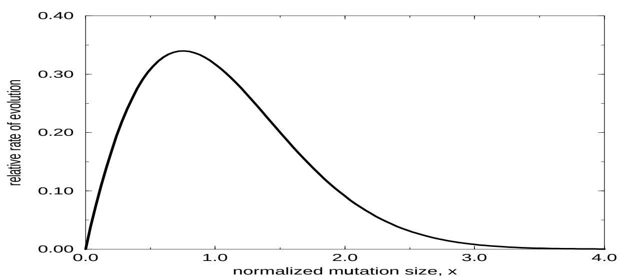

Figure 15: Rate of adaptive substitutions in Kimura's (1983) model

Orr's (1998) results on the distribution of factors fixed in the course of adaptation. Kimura's equation (21) gives the probability that factors of different size will contribute to the *next* adaptive substitutions. However, it does not take into account the fact that during adaptive evolution the distance to the optimum continuously decreases as favorable mutations get fixed. Thus, the size of the factor fixed on the next step is expected to be smaller than the size of the factor fixed on the previous step. For an advantageous mutation of size r, the expected displacement towards the optimum is approximately $r/\sqrt{n}$ (because $r^2 = x_1^2 + x_2^2 + \cdots + x_n^2$, the square of the displacement in a particular direction $x_1^2 \approx x^2/n$). Thus, if the initial distance to the optimum is one ($d = 2$), then the expected distance to the optimum after a favorable substitution is $1 - r/\sqrt{n} = 1 - 2x/n$. This shows that the expected distance to the optimum decreases by a constant proportion $1 - 2x/n$ each generation. The probability density of factors fixed at substitution i, $\psi(x, i)$, is approximately

$$\psi(x, i) = C\ 2cx(1 - \Phi(cx)),$$

where $c = (1 - 2x/n)^{1-i}$ and $C = 2c$ is the normalizing coefficient. The distribution of factors fixed during adaptation is found by summing up over the walk to the optimum:

$$\psi(x) = \frac{1}{k_L} \sum_{i=1}^{k_L} 4c^2 x(1 - \Phi(cx)),$$

where k_L is the last substitution considered. For large k_L, the last sum can be approximated by an integral after a change of variables ($t = cx$),

$$\psi(x) = -\frac{1}{\ln(1-f)}\ \frac{1}{x}\ \int_x^{x/(1-f)} 4t[1 - \Phi(t)]dt, \tag{22}$$

where f is the fraction of the distance to the optimum traveled ($1 - f = (1 - 2x/n)^{k_L} \approx exp(-2xk_L/n)$). Note that equation (16) is independent of dimension, n. Numerical studies of this equation show that the distribution of factors fixed during adaptation is approximately exponential:

$$\psi(x) \approx exp(-\lambda x).$$

(see Figure 16)).

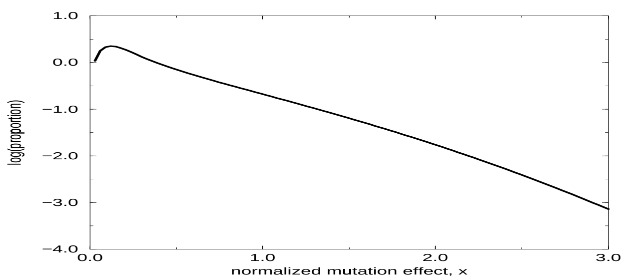

Figure 16: Distribution of factors fixed during adaptation in Orr's (1998) model with $f = 0.9$.

Orr's findings suggest high probability of fixing large factors especially initially. Also notice that the distribution of factors fixed does not resemble that assumed by the infinitesimal model (many loci with similar small effects). These conclusions are based on several assumptions (the adaptive landscape does not change, there is a lot of symmetry, deleterious mutations are not considered).

4.3 The waiting time to stochastic transition between peaks

The expected exit time. Let $T(z)$ be the time of exit from the interval (a, b) of a stochastic process $X(t)$ starting at $X(0) = z$. Let $M_{\delta z}$ and $V_{\delta z}$ be the expected average change and the expected variance of the stochastic process given $X = z$. Then, $T(z)$ satisfies to a linear homogeneous second order ordinary differential equation

$$M_{\delta z} T'(z) + \frac{1}{2} V_{\delta z} T''(z) = -1 \tag{23}$$

with boundary conditions $T(a) = 0, T(b) = 0$ (e.g., Kimura and Ohta 1969). [This is a Kolmogorov backward equation of diffusion theory.] The solution can be explicitly found by standard methods (e.g., the variation of parameters method). This solution is

$$T(z) = 2\int_a^z \frac{u}{V_{\delta x} F}\, dx + 2u(z)\left[\int_z^b \frac{dx}{V_{\delta x} F} - \int_a^b \frac{u}{V_{\delta x} F}\, dx\right] \tag{24}$$

where $u(z)$ is the probability that starting at z the stochastic process reaches b before reaching a,

$$u(z) = \frac{\int_a^z F(x)dx}{\int_a^b F(x)dx}, \tag{25}$$

and $F(x)$ is given by equation (7b).

Let us consider a diploid population of size N. Assume that a single additive quantitative trait z controls fitness $w(z)$. Let the distribution of the trait in the population has a constant variance P. In this model,

$$M_{\delta z} = P\, \frac{d \ln w}{dz}, \;\; V_{\delta z} = \frac{P}{N}$$

Assume that the fitness function $w(z)$ has two "peaks" at $z = a$ and $z = b$ with a "valley" between them at $x = \nu$ (see the Figure). If initially the population is at one peak, the expected time until the peak shift by random genetic drift is approximately

$$t = \frac{2\pi}{G} \; (-c_a c_\nu)^{-1/2} \left[\frac{\overline{w}(a)}{\overline{w}(\nu)} \right]^{2N} \tag{26}$$

where $\overline{w}(x)$ and $c_x = \overline{w}^{-1} \partial^2 \overline{w} / \partial \overline{x}^2$ are the average fitness of the population and the curvature of the fitness function at $z = x$ (Barton and Charlesworth 1984; Lande 1985). For example, if the initial adaptive peak is 1.05 times higher than the valley (that is if $\overline{w}(a)/\overline{w}(\nu) = 1.05$), then using realistic values of other parameters if $N = 100$ then $T \sim 10^6$ generations whereas if $N = 200$ then $T \sim 10^{10} - 10^{11}$ generations (Lande 1985). We conclude that stochastic transitions across valleys of maladaptation take an extremely long time.

5 Nearly neutral networks and holey adaptive landscapes

See Gavrilets (1997) and Gavrilets (200? - available from my web page) for introductory reviews.

Most biologists accept that the view of rugged adaptive landscape is more general than those of single-peak or flat landscapes. Although on a local scale (that is within a small subset of the genotype space) an adaptive landscape can be treated as single-peaked or flat, on a larger scale the picture of a rugged adaptive landscape appears much more plausible. There is, however, one feature implied by the view of rugged adaptive landscapes that can be questioned. This is the implicit assumption that adaptive peaks are "isolated" and that continuous evolution is impossible without crossing valleys of maladaptation. At the first sight, this assumption appears to be a vary natural one. Indeed, everybody knows from his or her own hiking experience that it is impossible to get from the top of one hill to another without having to descend to a kind of valley between them. Our intuition tells us that things will stay about the same in landscapes with many more dimensions than the three we are so well familiar with and that extended "ridges" connecting well-fit genotypes are very improbable. However, this intuition is simply wrong. As we will see in a moment, enormous dimensionality of the genotype space makes fitness "ridges" inevitable.

Table 3: Gene number (after Bird 1995)

Prokaryotes	1,000-8,000
Eukaryotes (except vertebrates)	7,000-15,000
Vertebrates	50,000-100,000

Genotypes are represented as sequences of genes. The dimensionality of the genotype space was defined as the number of new sequences that one can get from a sequence by changing single elements of the sequence. This is the same as the number of one-step neighbors each sequence has. Even the simplest organisms known have on the order of a thousand genes and on the order of a million DNA base pairs. Each of the genes can be at at least several different states (alleles). Thus, the dimensionality of genotype space is at least on the order of thousands. It is on the order of millions if one considers DNA base pairs instead of genes. This results in an astronomically large number of possible genotypes (or DNA sequences) which is much higher than the number of organisms present at any given time or even cumulatively since the origin of life. [Note that this was well recognized by Wright himself.] At the same time, the number of different fitness values is limited. For example, if the smallest fitness difference that one can measure (or that is important biologically) is, say, 0.001, then only 1000 meaningfully different fitness classes are possible. Assume that one wants to create an artificial adaptive landscape for a set of binary sequences in a computer memory by assigning a numerical fitness value between zero and one to each sequence. Under double precision each number a computer memory will be described by no more than 64 bits. This implies that the assignment of different numerical fitness values to different sequences is only possible for sequences with the length $L < 64$. For longer sequences one will just not have enough different numbers!

There are important consequences of this observation. Because of the many-to-one redundancy in the genotype-fitness map, different genotypes are bound to have very similar (identical from any practical point of view) fitnesses. Unless there is a strongly "non-random" assignment of fitnesses (say all well-fit genotypes are put together in a single "corner" of the genotype space), a possibility exists that well-fit genotypes might form connected clusters (or networks) of one-step neighbors that extend throughout the genotype space. If this were so, populations might evolve along these clusters by single substitutions and diverge genetically without ever going through any adaptive valleys.

A few notions relevant for this feature of the multidimensional adaptive landscapes will be important below. A **neutral network** is a contiguous set of sequences possessing the same fitness. [Here, the word "contiguous" will mean that any two sequences of the set can be connected by a chain of "one-step

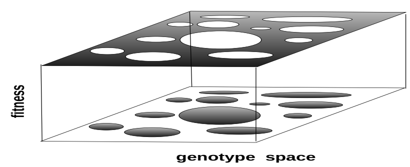

Figure 17: A holey adaptive landscape

neighbors" also belonging to the set.] A **nearly neutral network** is a contiguous set of sequences possessing approximately the same fitness. A **holey adaptive landscape** is an adaptive landscape where relatively infrequent well-fit (or as Wright put it, "harmonious") genotypes form a contiguous set that expands ("percolates") throughout the genotype space. An appropriate three-dimensional image of such an adaptive landscape is a flat surface with many holes representing genotypes that do not belong to the percolating set (see Figure 17). The flatness of the surface reflects close similarity between the fitnesses of the genotypes forming the corresponding nearly-neutral network.

The metaphor of holey adaptive landscapes emphasizes the ridges at the expense of other features of multidimensional adaptive landscapes. It puts the idea of alternative well-fit combinations genes explicit in the metaphor of rugged landscapes and the idea about the prevailing (nearly) neutral genetic changes explicit in the metaphor of flat landscapes within a single unifying picture. In this picture, local adaptation can be viewed as climbing from a hole towards a nearly neutral network of well-fit genotypes. The process of climbing is considered to occur at a shorter time scale than necessary for speciation and clade diversification. Overstating to make the point, within this metaphor peaks are largely irrelevant because the population is never able to climb there (due to the absence of right mutations and the high frequency of deleterious mutations pushing the population downhill). Valleys are largely irrelevant because natural selection will quickly remove populations from there. What is relevant are the ridges of well-fit genotypes that expand throughout the genotype space. Evolution along these ridges is the stuff of speciation and diversification. This view implies that most important substitutions are nearly neutral. It explains why there is no need to overcome strong natural selection to evolve (and speciate). The metaphor of holey adaptive landscapes identifies a simple reason for decoupling of micro- and macroevolution which is the fact that the relationship between genes (microevolution) and fitness and other characters (macroevolution) has a many-to-one nature. It provides a theoretical basis for Ohta's theory of nearly neutral evolution.

Below I illustrate the origin of (nearly) neutral networks and holey adaptive landscapes using two simple models.

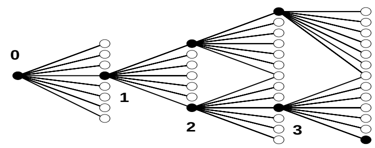

Figure 18: Branching on a hypercube. The figure presents a part of the genotype space for $L = 8$ loci. Black circles are viable genotypes. White circles are inviable genotypes.

5.1 Russian roulette model (Gavrilets and Gravner 1997)

Let us consider haploid individuals different with respect to L diallelic loci. Assume that genotype fitnesses are generated randomly and independently and are only equal to 1 (viable genotype) or zero (inviable genotype) with probabilities p and $1-p$, respectively. [Here, one might think of the set of all possible genotypes playing one round of Russian roulette with p being the probability to get a blank.] A counter-intuitive feature of this model is that viable genotypes form neutral networks in genotype space if $p > 1/L$ (in the limit of large L). It is very easy to see why this is so. Because there are L diallelic loci, each genotype has L one-step neighbors. Pick up a viable genotype, say genotype 0. If at least one of its one-step neighbors, say genotype 1, is viable, there is a neutral network with at least two genotypes (0 and 1). Next, we concentrate on genotype 1. It also has L one-step neighbors of which one is genotype 0. If at least one of the remaining $L-1$ one-step neighbors, say genotype 2, is viable, there is a neutral network with at least three genotypes (0, 1 and 2). Next, we concentrate on genotype 2. It also has L one-step neighbors of which one is genotype 1. If at least one of the remaining $L-1$ one-step neighbors, say genotype 3, is viable there is a neutral network with at least four genotypes (0, 1, 2 and 3). The point is that if there is one viable genotype out of $L-1$ one-step neighbors, the size of the neutral network increases by one. One can see that as $L \to \infty$, the probability of an infinite path started at genotype 0 is approximately the same as the probability of survival of the branching process with $L-1$ successors where each successor is viable with probability p (see Figure 18). The branching process does not die out if the expected number of viable successors, which is $p(L-1)$, is larger than one. Thus, a neutral network of viable genotypes expands throughout the genotype space if $p > 1/(L-1) \approx 1/L$. This means that the existence of an extensive neutral network in the Russian roulette model is guaranteed even for very small values of p if the number of loci L is sufficiently large!

[In evolutionary biology, mathematics is mostly used to formalize biological intuitions and to confirm or reject verbal arguments. New deep and unexpected insights coming from mathematics are less often. (examples: cycling and chaotic dynamics in population ecology models etc) The conclusion about the existence of nearly neutral networks is an example of such an insight.]

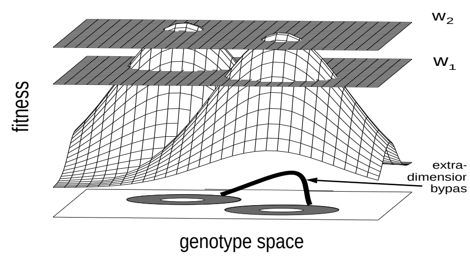

Figure 19: Percolating fitness band in a rugged landscape.

5.2 Uniform distribution of fitnesses

The assumption that fitness can only take two values might be viewed as a serious limitation. Here, I consider the same genotype space as in the previous section, but now I assume that genotype fitness, w, is a realization of a random variable having uniform distribution between 0 and 1. This is the same fitness landscape as analyzed by Kauffman and Levin (1987) in their study of adaptive walks on rugged adaptive landscapes. Let us introduce two threshold values, w_1 and w_2 such that $w_2 - w_1 = p > 0$, and let us say that a genotype belongs to a (w_1, w_2)-fitness band if its fitness w satisfies to a set of inequalities $w_1 < w \leq w_2$. According to the results from the previous section if L is large and $p > 1/L$, there is a "percolating" nearly neutral network of genotypes in a (w_1, w_2)-fitness band. The members of this network can be connected by a chain of single-gene substitutions resulting in genotypes that also belong to the network. If one chooses $w_2 = 1$ and $w_1 = 1 - p$, it follows that uniformly rugged landscapes have very high "ridges" (with genotype fitnesses between $1 - p$ and 1) that continuously extend throughout the genotype space. In this model, there is a percolating network of well-fit genotypes and, thus, the corresponding adaptive landscape is holey (Gavrilets and Gravner 1997). In a similar way, if one chooses $w_2 = p$ and $w_1 = 0$, it follows that uniformly rugged landscapes have very deep "gorges" (with genotype fitnesses between 0 and p) that also continuously extend throughout the genotype space. If p is small, the fitnesses of the genotypes in the (w_1, w_2)-fitness band will be very similar. Thus, with large L extensive evolutionary changes can occur in a nearly-neutral fashion via single substitutions along the corresponding nearly-neutral network of genotype belonging to a percolating cluster. The maximum number of the non-overlapping (w_1, w_2)-fitness bands is $1/p$, which with p just above the percolation threshold is about L. Thus, the maximum number of non-overlapping near-neutral networks of genotypes percolating throughout the genotype space is approximately L.

5.3 Deterministic evolution on a holey landscape: genetic canalization

The topology of the (nearly) neutral network controls the properties of evolutionary dynamics. To illustrate this we will consider evolutionary dynamics of an infinite asexual population in the Russian roulette model. We will follow van Nimwegen et al. (1999).

Let w_i be the fitness of genotype i ($w_i = 1$ or $w_i = 0$). Only the frequencies of viable genotypes (with fitness $w_i = 1$), which we denote by as x_i, will be important below. After selection $x_i' = (w_i/\overline{w})x_i = x_i/\overline{w}$, where $\overline{w}$ is the average fitness of the population. After mutation

$$x_i'' = (1-\mu_i)x_i' + \sum_{j\epsilon V} \mu_{ji} x_j',$$

where μ_i is the probability that genotype i mutates to a different genotype, μ_{ji} is the probability that genotype j mutates to genotype i, and V is the set of viable genotypes. In the above equation, the first term gives the frequency of the genotypes i that did not mutate and the second term gives the frequency of genotypes i formed by mutation of other viable genotypes.

Let each genotype have L one-step neighbors. Assume also that mutations at different sites have equal probabilities and disregard the probability of more than one mutation per genotype. Then $\mu_i = \mu$ and $\mu_{ji} = \mu/L$ if the genotypes j and i are one-step neighbors and is zero otherwise. In this case, the equilibrium genotype frequencies are solutions of the simultaneous equations

$$x_i = (1-\mu)\frac{1}{\overline{w}}\, x_i + \frac{\mu}{L} \sum_{j\epsilon M_i} \frac{1}{\overline{w}}\, x_j, \tag{27}$$

where M_i is the set of viable neighbors of genotype i.

Let v_i be the probability that genotype i does not mutate to an inviable state. If n_i is the number of viable one-step neighbors for genotype i and $L - n_i$ is the number of inviable one-step neighbors, then under the mutation scheme used here,

$$v_i = 1 - \mu\, \frac{L - n_i}{L}.$$

At equilibrium, the mean fitness of the population $\overline{w}$ must be equal to the probability $\overline{v}$ that a randomly chosen viable genotype does not mutate to an inviable state, $\overline{v} = \sum v_i x_i / \sum x_i$. Using the equation above, it follows that

$$\overline{w} = \overline{v} = 1 - \mu + \mu\, \frac{\overline{n}}{L},$$

where $\overline{n} = \sum n_i x_i / \sum x_i$ is the "population neutrality" that is the average number of viable one-step neighbors. Note that the genetic load $L = 1 - \overline{w} = \mu(1 - \overline{n}/L)$ decreases with increasing the population neutrality $\overline{n}$. The above relation between $\overline{w}$ and $\overline{n}$ allows one to represent equations (27) as $\overline{n}x_i = \sum_{j\epsilon M_i} x_j$ which in turn can be written in matrix notation as

$$Mx = \overline{n}x, \tag{28}$$

where $x = (x_1, x_2, \dots)^T$ is the vector of genotype frequencies and M is the adjacency matrix for the network of viable genotypes. [The element M_{ij} of this matrix is equal to one if the genotypes i and j are one-step neighbors and is equal to zero otherwise.]

Because matrix G is non-negative and the network of viable genotypes is connected, matrix G is irreducible. Therefore, it has a single positive eigenvector corresponding to the largest positive eigenvalue which give the equilibrium values of x and $\overline{n}$, respectively. Thus, both the equilibrium population genetic structure (characterized be the vector of genotype frequencies x) and the average number of viable neighbors (characterized by $\overline{n}$) are functions only of the topology of the network of viable genotypes as determined by the adjacency matrix M.

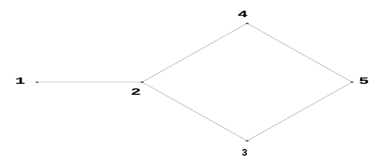

Figure 20: An example of a neutral network of viable genotypes.

Example

Let us consider a network of viable genotypes depicted in Figure (21). The corresponding adjacency matrix is

$$G = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 \end{pmatrix}$$

The largest eigenvalue of this matrix is $\overline{n} = 2.14$ and the corresponding normalized eigenvector is $(0.12, 0.26, 0.21, 0.21, 0.20)$. This shows that the population neutrality at mutation-selection balance $\overline{n}$ is larger than the "network neutrality" (that is the average number of viable neighbors in the neutral network described by the adjacency matrix M) which is equal to two. One can also see that genotypes with more neutral neighbors are more common than genotypes with smaller number of viable neighbors. For example, the frequency of genotype 2 which has three one-step neighbors is 0.26 and is larger than the frequencies of genotypes 3,4 and 5 which have two one-step neighbors each and is larger than the frequency 0.12 of genotype 1 which has only one neighbor. Thus, the population moves into the areas of genotype space with high concentration of viable genotype. One of the consequences of this is reduced probability of deleterious mutation that is *genetic canalization.* These observations appear to be rather general.

5.4 Speciation on a holey landscape: The Bateson-Dobzhansky-Muller (BDM) model

The models of evolution on rugged adaptive landscapes have not been very successful in describing speciation. A major problem is that in these models populations have to overcome selection to speciate which cannot happen easily. However, evolution of reproductive isolation does not necessarily have to be opposed by selection. As first shown by Bateson (1909), Dobzhansky (1936, 1937) and Muller (1940, 1942) reproductive isolation can result after a series of genetic substitutions each of which is not opposed by selection. For example, reproductive isolation will follow if different populations that were initially identical genetically experience substitutions at different loci and the derived alleles (or genotypes) happen to be "incompatible." To illustrate this, let us consider a two-locus two-allele model with alleles **A** and **a** at the first locus and alleles **B** and **b** at the second locus. Assume that alleles **a** and **B** are incompatible in the sense that all organisms having these two alleles simultaneously are inviable or sterile. Let there be two geographically isolated populations initially monomorphic for genotype **AAbb**. Now if in one population, allele **A** is substituted (by mutation, random genetic drift, selection, etc) for allele **a** and in the other population, allele **b** is substituted for allele **B**, the resulting populations will be reproductively isolated (see Figure 21). Alternatively, if both populations are initially monomorphic for genotype **aabb**,

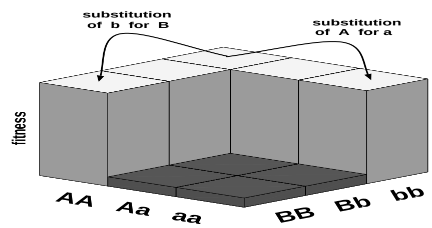

Figure 21: Adaptive landscape in the two-locus two-allele Dobzhansky model. Alleles **a** and **B** are incompatible. The arrows specify the chain of gene substitutions leading to complete reproductive isolation.

then speciation will follow if one of them experiences two substitutions: first, of allele **a** for allele **A** and then of allele **b** for allele **B**.

Long time ago Dobzhansky observed that "this scheme may appear fanciful, but it is worth considering further since it is supported by some-well established facts and contradicted by none" (p. 282). The model has both an attractive simplicity and an intuitive appeal. Indeed, "the loss in fitness to species hybrids is no more surprising than the fact that a carburetor from a car manufactured in the U.S.A. does not function in an engine made in Japan" (Charlesworth 1990, p. 103). By now, the BDM model is widely accepted and is supported by a growing amount of data (refs). The BDM model provides a basis for describing reproductive isolation due to natural and sexual selection. In fact, all existing models of sexual selection explicitly incorporate the genes (or traits) that are perfect in a right genetic (or phenotypic) background but become "incompatible" when brought together. Thus, sexual selection can be interpreted in terms of the BDM model.

Below I will follow Gavrilets (2000).

5.4.1 Allopatric speciation in the BDM model

Let us consider an isolated population that starts with haplotype **ab** fixed and evolves to the state with haplotype **AB** by fixing allele **B** first, and then fixing allele **A**. Assume that mutations $\mathbf{a} \rightarrow \mathbf{A}$ and $\mathbf{b} \rightarrow \mathbf{B}$ are irreversible and have rate μ per generation. With no selection for local adaptation, the process of fixation on an allele is neutral. The average waiting time to fixation of a neutral allele given it is initially absent is $1/\mu$ (e.g., Nei 1976). Because the population needs to fix two mutations, the average waiting time to speciation, t, is approximately

$$t = \frac{2}{\mu}. \tag{29}$$

In principle, it is possible that alleles **A** and **B** have selective advantage over alleles **a** and **b** (for example, due to pleiotropy etc). Let N be the population size. The number of mutations per generation is $2N\mu$. The probability that an advantageous mutation is fixed is approximately $2s/(1 - exp(-4Ns))$ (Kimura 1983). Thus, the average rate of fixation is $\mu\ S/(1 - exp(-S))$ where $S = 4Ns$. This results in the average waiting time to speciation being approximately

$$t = \frac{2}{\mu}\ \frac{1 - exp(-S)}{S}. \tag{30}$$

For example, increasing S from 0 to 10 decreases the waiting time to speciation to approximately 1/10 of that in the case of no selection for local adaptation.

5.4.2 Parapatric speciation in the BDM model

Let us consider a finite population of sexual organisms with discrete non-overlapping generations. The population is subject to immigration from another population. For example, one can think of a peripheral population (or an island) receiving immigrants from a central population (or the mainland). All immigrants are homozygous and have a fixed "ancestral" haplotype **ab**. Mutation supplies new alleles **A** and **B** which may be fixed by random genetic drift and/or selection for local adaptation. Migration brings ancestral genes. As before we assume that alleles **b** and **A** are incompatible. Speciation occurs when genotype **AB** gets fixed.

I will use a weak mutation and weak migration approximation neglecting within-population variation (refs). Under this approximation the only role of mutation and migration is to introduce new alleles which quickly get fixed or lost. The dynamics of speciation in this model can be modeled as a random walk on a set of states $0, 1, 2$, where state 0 corresponds to a population fixed for the ancestral haplotype **ab**, state 1 corresponds to a population fixed for the "intermediate" haplotype **Ab**, and state 2 corresponds to a population with haplotype **AB** fixed. Reaching state 2 represents a speciation event.

We wish to estimate the average time to speciation t, defined as the average time to reach state 2 starting from state 0. In the process of evolution towards speciation will be many unsuccessful speciation attempts when the population will substitute **a** for **A** only to lose it and return to the ancestral state. Another important characteristic is the average duration of speciation, T, defined as the time it takes to get from the ancestral state ($d = 0$) to the state to complete reproductive isolation ($d = 2$) without returning to the ancestral state. [Duration of speciation is the duration of intermediate forms in the actual transition to a state of complete reproductive isolation. Duration of speciation is similar to the conditional time that a new allele destined to be fixed segregates before fixation.]

No selection for local adaptation. Assume that there is no selection for local adaptation. Let μ be the mutation rate per locus per generation. The process of fixation is approximately neutral with the probability of fixation of an allele being equal to its initial frequency. Thus, the transition rates from state 0 to state 1, and from state 1 to state 2 are equal to the mutation rate μ, and the transition rate from state 1 to state 0 is equal to the migration rate m. In this model, the average waiting time to speciation t and the average duration of speciation T can be easily found. They are

$$t = \frac{1}{\mu}\ (2 + R) \approx \frac{m}{\mu^2}, \tag{31a}$$

$$T = \frac{1}{\mu}\ \frac{2 + R}{1 + R} \approx \frac{1}{\mu}, \tag{31b}$$

where $R = m/\mu$ characterizes the strength of migration relative to that of mutation, and the approximation is valid if $R >> 1$. For example, if $m = 0.01$ and $\mu = 10^{-5}$, then $t_0 \approx 10^8$ generations and $T_0 \approx 10^5$ generations.

Equation (31a). Let us consider a Markov chain with $K+1$ states $0, 1, \ldots, K, K+1$. Let p_{ij} be the transition probability from state i to state j. We assume that the state $K+1$ is absorbing but the state 0 is not. Let t_i be the average time till absorption starting from i. The mean absorption times satisfy to the general system of linear equations

$$t_i = 1 + \sum_j p_{ij} t_j \tag{32}$$

for $i = 0, 1, \ldots, K$ with $t_{K+1} = 0$ (e.g., Norris 1997). Let t_i be the average time till absorption at 2 starting from i ($i = 0, 1$). Then, the times to absorption satisfy to a system of linear equations

$$\begin{aligned} t_0 &= 1 + (1-\lambda_0)t_0 + \lambda_0 t_1, \\ t_1 &= 1 + \mu_1 t_0 + (1 - \lambda_1 - \mu_1)t_1. \end{aligned}$$

Solving this system, one finds that

$$t_0 = \frac{1}{\lambda_1} + \frac{\mu_1 + \lambda_1}{\lambda_0 \lambda_1},$$

which simplifies to equation (31a).

Equation (31b). For the model under consideration

$$T_0 = \frac{1}{\lambda_0} + \frac{1}{\mu_1 + \lambda_1} \tag{33}$$

In this equation, the first term is the average time spent in state 0 before moving to state 1. The second term is the conditional average time, T_1^*, spent in state 1 before moving to state 2. The unconditional probability to move from state 1 to state 2 during time interval $(t, t+dt)$ is

$$P \equiv Pr(1 \to 2 \text{ during } (t, t+dt)) = e^{-(\lambda_1+\mu_1)t}\ \lambda_1 dt.$$

(Because the process is exponential, $exp[-(\lambda_1 + \mu_1)t]$ is the probability to spent at least time t at state 1 after moving there). The conditional probability is

$$\begin{aligned} P^* &\equiv Pr(1 \to 2 \text{ during } (t, t+dt) \mid \text{absorbed at } 2) \\ &= \frac{Pr(1 \to 2 \text{ during } (t, t+dt) \text{ and absorbed at } 2)}{Pr(\text{absorbed at } 2)} \\ &= \frac{e^{-(\lambda_1+\mu_1)t}\ \lambda_1 dt}{\lambda_1/(\lambda_1+\mu_1)} = e^{-(\lambda_1+\mu_1)t}\ (\lambda_1+\mu_1)dt, \end{aligned}$$

where $\lambda_1/(\lambda_1 + \mu_1)$ is the probability of absorption at state 2. The conditional average time is found as

$$T_1^* = \int_0^\infty t P^* dt = \frac{1}{\lambda_1 + \mu_1}.$$

Note a counter-intuitive result that the conditional average time to hit state 2 is the same as the unconditional average time spent in state 1.

Selection for local adaptation. Let us assume that new alleles **A** and **B** have selective advantage over ancestral alleles **a** and **b**. Let N be the population size. The number of mutations per locus per generation is $2N\mu$. The probability that an advantageous mutation is fixed is approximately $2s/(1 - exp(-4Ns))$. Thus, the transition probabilities from state 0 to state 1 and from state 1 to state 2 are $\mu S/(1 - exp(-S))$, where $S = 4Ns$. For a population at state 1, the number of ancestral alleles **a** brought by migration is $2Nm$. These alleles are deleterious in the environment the population inhabits; the corresponding probability of fixation is $2s/(exp(4Ns) - 1)$ (Kimura 1983). Thus, the probability of transition from state 1 to state 0 is $mS/(exp(S) - 1)$. The average waiting time to speciation and the average durations of speciation are

$$t_0 = \frac{1}{\mu}\ (2+R)\ \frac{1-e^{-S}}{S} \approx \frac{m}{\mu^2}\ e^{-S}\ \frac{1-e^{-S}}{S}, \tag{34a}$$

$$T_0 = \frac{1}{\mu}\ \frac{2+R}{1+R}\ \frac{1-e^{-S}}{S} \approx \frac{1}{\mu}\ \frac{1-e^{-S}}{S}, \tag{34b}$$

where $R = m/(\mu e^S)$ characterizes the strength of migration relative to that of mutation and selection, and the approximations are good if $R >> 1$. Even relatively weak selection for local adaptation can decrease t_0 by orders of magnitude. For example, with $S = 1$ and the same values of m and μ as above, $t_0 \approx 2.34 \times 10^7$ generations, $T_0 \approx 6.34 \times 10^4$ generations; with $S = 3$, $t_0 \approx 1.64 \times 10^6$ generations, $T_0 \approx 3.23 \times 10^4$ generations, and with $S = 5$, $t_0 \approx 1.73 \times 10^5$ generations, $T_0 \approx 2.24 \times 10^4$ generations. Note that the duration of speciation is much shorter than the waiting time to speciation:

$$\frac{T}{t} = 1/(1+R). \tag{35}$$

where R is typically large. For example, with the same parameter values as above $R = 368, 50$ and 7 (for $S = 1, 3$ and 5, respectively).

Because the waiting time to speciation in the two-locus Dobzhansky model scales as one over the mutation rate per locus squared, this time is rather long. However, the overall number of loci involved in the initial stages of reproductive isolation is at least on the order of tens to hundreds (e.g. Singh 1990; Wu & Palopoli 1994; Coyne & Orr 1998; Naveira and Masida 1998). This increases the overall mutation rate and can make speciation much more rapid.

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