Chapter 2.1. Populations and Tools for Studying Them

Chapter 2.1 introduces a number of concepts that are required to understand Microevolution. Central among them is population, because Microevolution is just a word for changes of genetic compositions of populations. Other concepts are concerned with small-scale properties of fitness landscapes, which are essential for the key factor of Microevolution, natural selection, and with statistical and dynamical methods of studying variable populations.

Section 2.1.1 presents the concept of population, broadly understood as a minimal set of individuals such that descendants of at least some of them will be around even in remote future generations and will not possess genes from the outsiders. A viable lineage must be represented, at almost every moment, by the population of a substantial size. However, boundaries between populations are often fuzzy. Studies of life at the level of populations involve several simplifications, which makes population biology very successful within its domain of applicability.

Section 2.1.2 considers fitness landscapes at the small scale of within-population variation. At this scale, fitness landscapes are relatively simple, mostly lacking multiple peaks. Thus, quantitative features of fitness landscapes become crucial. Two concepts, fitness potential and epistasis, are introduced to describe such features. Simultaneous consideration of the fitness landscape and of the population on it leads to a natural classification of fundamental modes of selection.

Section 2.1.3 deals with describing and of assaying variation among individuals within a population. Individuals can be characterized by structureless, quantitative, or complex traits. Most of within-population genetic variation can be naturally resolved into simple, distinct traits, and a simplified description of variation is often sufficient to understand a particular aspect of Microevolution. A variable population can be thought of as a point within the space of possible population compositions. Assaying variation consists of two steps. First, genotypes and/or phenotypes of some number of individuals, sampled from the population, are studied experimentally. After this, properties of the whole population must be inferred statistically from this sample.

Section 2.1.4 presents basic concepts that are necessary to study dynamics of any object, including populations: phase space, dynamical model and its comprehensive solution, transformation law, attractors and stability, and parameters and bifurcations are

introduced informally. These concepts are introduced using the key Microevolutionary process, selection-driven allele replacement, as an example. Direct and inverse problems of population dynamics and approaches to building dynamical models of Microevolution are discussed.

Chapter 2.1 is based on several concepts first presented in Introduction and on mathematical techniques which were already encountered in Chapters 1.1 and 1.2, and constitutes the foundation for treatment of Microevolution in Chapters 2.2-2.6.

Section 2.1.1. Population as object of Microevolution

Individuals, and even lineages of descent of apomictic individuals, are ephemeral. Moreover, with amphimixis there are no individual lineages of descent. Thus, as long as a long-term process, such as evolution, is to be studied, we need to consider many individuals together. A population of apomicts is a set of individuals that currently represents the minimal durable set of genome-level lineages of descent, such that at least one of these lineages will persist for a long time. A population of amphimicts can be viewed either as a minimal set of individuals that include all possible ancestors for the descendants of each of them or as a minimal durable set of locus-level lineages of descent. Unless a lineage is represented, at almost every moment, by a population of a substantial size, it will soon go extinct due to inefficient selection. The same pair of individuals may belong either to the same or to different populations, depending on the time scale of a process we wish to study. Studies of long-term Microevolution often require considering the most inclusive populations, whose boundaries coincide with boundaries of species. Some natural populations are essentially structureless, while others have well-developed spatial structures. Biology at the population level is relatively simple, because it ignores internal structure of organisms. This simplicity makes the populational approach productive when changes of population sizes or genotype frequencies are of interest, but, at the same time, makes it unsuitable for studying Macroevolution of complex phenotypes.

2.1.1.1. What is a population of apomicts?

Nobody is without peers: every individual lives alongside many other, similar individuals. Thus, one of the key concepts of evolutionary biology, population, may appear to be straightforward. Indeed, all wolfs living in the same forest obviously belong to the same population, while wolfs and bears, or wolfs from different continents, do not. Generally, all similar individuals that live together, compete for resources and, if their reproduction is amphimictic, breed with each other, constitute a population. This simplistic view, adopted so far, is essentially correct, but a more careful look at the concept of population is still useful.

For a start, let us define population vaguely, as a minimal set of individuals that must be considered together, in order to study Microevolution. Here, of course, comes a question: why cannot we treat each individual separately? In particular, if reproduction is apomictic, which will be our assumption for now, every current individual initiates its own ancestor-descendant lineage. So, can we deal with one apomictic lineage at a time?

The answer to this question is "no", due to a very fundamental reason: an individual lineage is usually short-lived. Thus, if we want to deal with a durable object, which is necessary for studying slow evolution, considering any one lineage in isolation is insufficient. Only a set of lineages, represented, at each moment, by a set of individuals, may provide us with such an object.

The ephemeral nature of individual lineages may seem paradoxical. Imagine an isolated pond, populated, among other things, by a large number N (say, a billion) of obligately apomictic bdelloid rotifers *Philodina roseola* (Fig. 2.1.1.1a). Surely, individuals are ephemeral, but can we expect a large proportion of them to contribute to even remote generations?

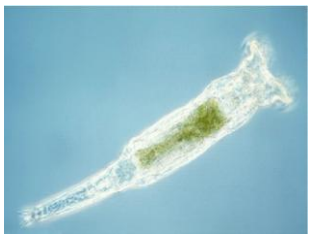

Fig. 2.1.1.1a. An apomictic bdelloid rotifer *Philodina roseola*. www.mcb.harvard.edu/Meselson/Proseola.jpg

Indeed, if each individual always leave exactly one offspring, this would be the case and our rotifers would exist forever as a constant-size bundle of immortal lineages (paint them purple; Fig. 2.1.1.1b), each of which could be perhaps considered separately. However, this situation is unrealistic, as any rotifer may easily leave no offspring. Thus, lineages of almost all current individuals will go extinct in a few generations. Eventually, the descendants of a single individual (paint her and her offspring red) will take over the pond, and will multiply to a billion individuals, assuming that N remains constant. Conversely, all other lineages (paint them blue) will perish (Fig. 2.1.1.1b). Since we cannot *a priori* pick the eventual winner, we must consider together all the rotifers currently living in the pond, although almost all of them represent doomed lineages.

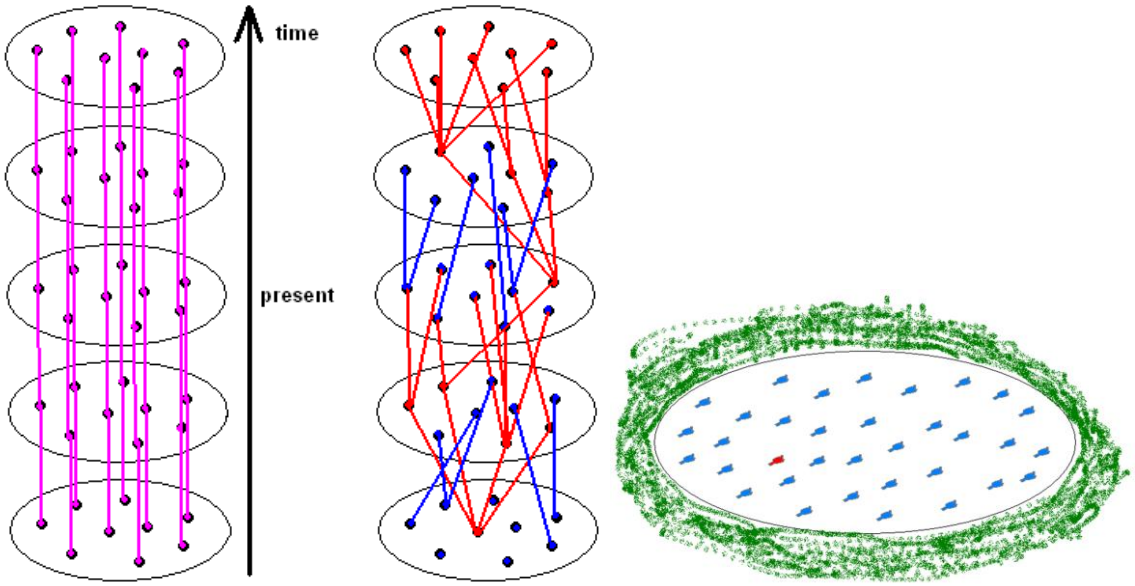

Fig. 2.1.1.1b. An unrealistic situation when lineages of all current individuals persist forever (left). A realistic situation when lineages die out and multiply, until just one of them replaces all others (center). The rotifer whose offspring will eventually replace that of all others (red) cannot be identified, within the pond, among her peers (blue) (right).

The same, of course, is true if we go backward in time: a billion of lineages corresponding to current individuals coalesce with each other and, at some moment in the past, merge into a single lineage, represented then by an individual (red among the blues) who gave rise to the whole current population (Fig. 2.1.1.1b). As long as conditions remain invariant, the number of generations since the most recent common ancestor

(MRCA) of all current individuals is, on average, equal to the number of generations until all but one of the current lineages become extinct. Indeed, if there is nothing special about the current generation, the processes of branching and extinction of lineages, if we look forward, and of their coalescence, if we look backward, proceed at the same speed.

Why is life so unfair? One obvious reason is natural selection, *i. e*. variation in fitness, the expected per individual number of offspring, among lineages (Section 2.3.2). Such variation, caused by different hereditary properties of lineages, is always present. Every lineage with a substantially reduced fitness will certainly go extinct soon, unless it initial frequency is very close to 1.

Moreover, life would remain unfair even without selection, due to stochasticity of the process of reproduction, which causes random drift (Section 2.2.5). Let us consider the dynamics of one lineage, with the expected number of offspring of each individual being 1. If we assume that every individual leaves exactly 1 offspring, the lineage will consist of exactly one individual at every generation and will never go extinct. However, even a slight violation of this unrealistic assumption changes the situation qualitatively. Suppose, for example, that an individual leaves 0, 1, and 2 offspring with probabilities 0.1, 0.8, and 0.1, respectively. Then, a lineage will almost certainly go extinct in 1000 generations, but, if this does not happen, it will be expected to consist of many individuals. Indeed, the expected total number of individuals in our lineage is always 1, so that if the probability of its extinction, by some generation, is p, the expected number of individuals in this generation, provided that extinction did not occur, is $T = 1/(1-p)$, which yields the expected number of individuals $0p + T(1-p) = 1$. With time, p approaches 1 and, conversely, T approaches infinity, as long as nothing checks an unlimited expansion of the lineage (Fig. 2.1.1.1c).

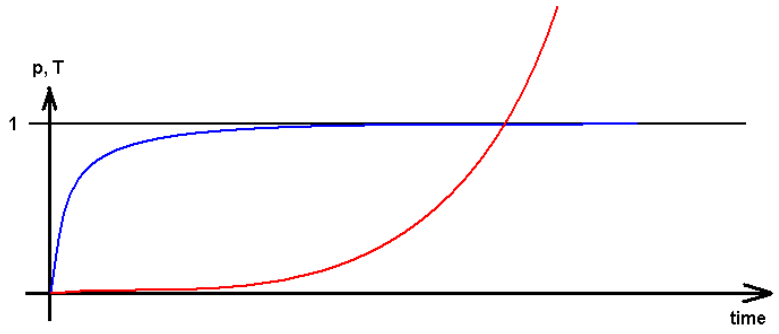

Fig. 2.1.1.1c. Dynamics of a branching process that describes a lineage, initiated from one individual, where each individual is expected to leave 1 offspring. Probability of extinction p (blue), and the expected number of individuals, provided that extinction did not occur, T = 1/(1-p) (red) are shown as functions of the number of generations assuming that there is some random variation in the number of offspring per individual.

Quantitative analysis of genealogies (a term commonly used for within-population phylogenies, Section 1.1.3) of lineages that appear due to random drift shows that with a biologically reasonable variance in the number of offspring per individual, the expected time until extinction of all equally fit lineages except one in a population of constant size N is 2N, and more than one lineage rarely lingers for over 10N generations (Fig. 2.1.1.1d; Section 2.3.5). Thus, even without selection, random drift slowly leads to replacement of the set of lineages with just one of its members. Even a lineage with the highest fitness can become extinct accidentally, while it is still represented by a small number of individuals, but its chances of replacing all others are the highest, and this can happen fast. A lineage with selective advantage s (in the sense those who belong to this lineage leave, on average, 1+s offspring for each 1 offspring left by anybody else) will become fixed after only ~log(N/s) generations, provided that it escaped early accidental extinction (Section 2.4.1).

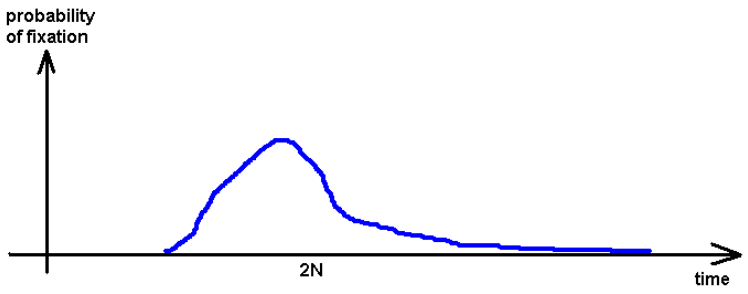

Fig. 2.1.1.1d. Distribution of the number of generations until one lineage displaces all others in a population of constant size N, assuming that the distribution of the number of offspring per individual is Poisson with parameter 1.

In natural populations, the MRCA of all currently present genotypes (or alleles, if we are dealing with amphimicts, see below) typically lived only ~10^4-10^6 generations

ago, even when individuals are small, like rotifers, and N is huge. Apparently, selection plays a large role in extinction-expansion dynamics of lineages in nature (Chapter 2.5).

So far, we assumed that only the overall number of individuals N is regulated, ensuring the long-term persistence of the population. Under this assumption, the expected per individual number of offspring must decline in the same way in all lineages when N becomes too high, due to a stronger competition. Conversely, if N drops because many lineages went extinct, the expected number of offspring in the remaining lineages will go up. Thus, the overall number of individuals will remain approximately constant, fluctuating within some bounds, which are determined by the carrying capacity of the environment.

Regulation of only the overall number of individuals is to be expected if all the lineages are ecologically equivalent, or, in other words, occupy the same ecological niche and compete for the same resources. Naturally, such regulation does nothing to protects individual lineages against each other. Instead, it creates a zero-sum game of survival among lineages: one lineages' gain is everybody else's loss. Impossibility of stable coexistence of ecologically equivalent lineages is known as Competitive Exclusion or Gauze principle.

Thus, we are ready to define a population of apomicts as **the minimal set of individuals which currently represents a durable set of lineages, such that at least one of these lineages will likely persist for a long time**. Obviously, we have to include into this set all individuals whose offspring will play zero-sum game of survival, *i. e*. are ecologically equivalent and have a chance to encounter each other and compete. Thus, population is also **the most inclusive set of currently living individuals which represent lineages that are not protected against each other, so that expansion of one of them must be eventually accompanied by extinction of the others**. Of course, these two definitions are equivalent.

In contrast, independent regulation of the numbers of individuals that represent different lineages prevents one of them from displacing all others. Suppose that our rotifers are, in fact, of two ecologically distinct kinds, 1 and 2, that utilize different resources, due to their different genotypes. Then, if rotifers of kind 1 become rare, they will encounter less competition and, thus, will reproduce faster than those of kind 2 (and *vice versa*). As a result, rotifers of kinds 1 and 2 will always coexist, and at least two

current lineages will always be present. In other words, rotifers of kind 1 and of kind 2 constitute separate, coexisting populations. Sometimes we can directly observe the origin of ecological non-equivalence within a population, which leads to its split into two independently evolving populations, capable of indefinite coexistence (Chapter 1.6).

Individuals that belong to the same population must usually be genetically similar to each other. Indeed, all within-population genetic differences accumulated since a not-too-remote moment when all the currently present lineages coalesce to their MRCA. Even if a situation in which ecologically equivalent but genetically distinct organisms live together appears somehow, soon only a single kind will be left, restoring homogeneity.

One may wonder whether ecological equivalence of substantially different genotypes is feasible. Surprisingly, it is. Individuals of one species often outcompete and eliminate individuals of a clearly distinct species under experimental conditions. Of course, complete elimination of a species by a distinct competitor must usually be a rare event in nature: if common, such events would cause rapid decline of the overall diversity of life, because evolution can replenish it only slowly. Still, local extinctions of individuals of one species due to interspecies competition appear to be common in nature. Moreover, we often see a native species being driven to complete extinction by a successful invader; although the current outbreak of human-caused invasions is a historically unique situation (Section 1.5.3).

Thus, ecological and genetic similarity go together. Genetic similarity causes ecological similarity directly, and ecological similarity causes genetic similarity indirectly, due to coalescence of lineages. As a result, members of the same population are usually tightly related to each other, and, thus, are also similar, connected, and compatible to each other.

2.1.1.2. What is a population of amphimicts?

Obligate apomixis is relatively rare, and amphimixis, reproduction that involves regular genetic exchanges between individuals (Section 2.3.3), is ubiquitous. Obviously, amphimixis abolishes distinct ancestor-descendent lineages, as far as individuals and their complete genotypes are concerned, and uncouples the fates of different segments, or loci, of the same genotype. A genotype may be represented in the future only by its allele

at one locus, perhaps present in many descendants of the corresponding individual, while alleles at all its other loci will be lost. One can say that amphimixis creates a two-level object, consisting of individuals at the higher level and of loci at the lower level. Both these levels can be used to define amphimictic populations.

The need to consider populations, instead of individuals, is even more obvious with amphimixis than with apomixis: in the case of outcrossing, individual amphimicts cannot even reproduce. Thus, at the higher level of individuals, an amphimictic population is a reproductively closed set of individuals, *i. e*. the **minimal set of individuals such that even a remote descendant of each of them will have, among its other ancestors in the current generation, only those individuals that also belong to the same set** (Fig. 2.1.1.2a). Obviously, under this definition, two individuals belong to the same population if they, or their not-too-remote offspring, have a substantial probability of interbreeding. Thus, it may seem that populations of apomicts and of amphimicts are totally different notions. However, this is not really the case.

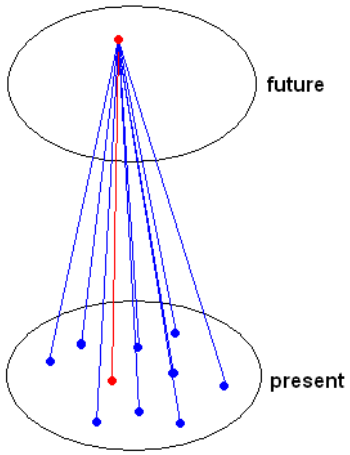

Fig. 2.1.1.2a. The individual-level definition of population of amphimicts. Consider an arbitrary individual and its descendant in a remote enough future generation (red). Those, and only those, current individual whose genes can also contribute to this offspring belong to the same population with this individual.

Indeed, at the lower level of loci, distinct lineages still exist for long time under amphimixis, being only very slowly eroded by recombination. If recombination is absent within a genome segment, or if each nucleotide site is treated as a separate locus, locus-

level ancestor-descendant lineages remain distinct forever, unless mutations that affect the genotype length (deletions, insertions, etc.) blur the very identity of sites. As it was the case for the whole-genotype lineages with apomixis, locus-level lineages with amphimixis do not coexist indefinitely but displace each other, due to the same reason: different self-reproducing entities, either individuals or alleles, produce different numbers of copies.

Due to recombination, different loci within a set of amphimictic individuals with shared ancestry can be traced back to different MRCAs that lived at different moments in the past. In the case of humans, mitochondrial Eve, a women from whom all modern humans inherited their mitochondrial DNAs, was, in all probability, not married to Y-chromosome Adam, a man from whom all modern men inherited their Y-chromosomes. Most likely, these two individuals lived thousands of kilometers and years apart, alongside many other ancient individuals, from some of whom all modern humans inherited particular segments of their autosomes and X-chromosomes (Fig. 2.1.1.2b).

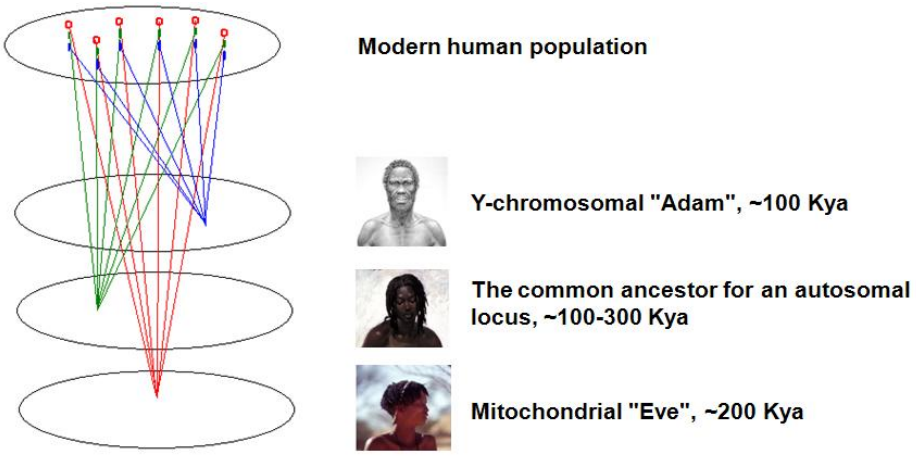

Fig. 2.1.1.2b. With amphimixis, ancestor-descendant relationships are different for different loci (blue, green, and red), and each locus-level lineage undergoes the process of extinction and expansion more or less independently and has its own MRCA.

Recombination within a chromosome makes locations of boundaries between segments that can be traced back to different MRCAs unpredictable. The characteristic length of a genotype segment that originated from a particular MRCA depends on how rapidly locus-level lineages displace each other and how rapidly they are eroded by

recombination. Among humans, this length is ~10,000 nucleotides, implying 10^5 segments with different MRCAs for 23 human chromosomes. The MRCA for almost every human genome segment lived 10,000-100,000 generations ago. In *Drosophila melanogaseter*, genome segments that share the same MRCA are ~10 times shorter and these MRCAs are more ancient, due to a slower lineage displacements in a larger population of flies (Section 2.3.5). Of course, alleles of the genome segment that originated from the same MRCA can be different from each other, due to post-MRCA mutations.

Thus, at the lower level of loci, an amphimictic population is a **set of individuals which, for each locus, currently represents the minimal durable set of locus-level lineages, such that at least one of these lineages will likely persist for a long time (**Fig. 2.1.1.1b). Another way of saying essentially the same thing is to define an amphimictic population as a **set of individuals which currently represents the minimal durable set of genotypes, such that genotypes that consist exclusively of alleles from these genotypes will likely persist for a long time (**Fig. 2.1.1.2b). In yet other words, an amphimictic population is **a set of individuals which currently represent the minimal durable gene pool, such that, at each locus, an allele from at least one of them will likely persist for a long time**.

These two approaches to the notion of amphimictic population, based on interbreeding of individuals and on survival of distinct locus-level lineages, usually lead to recognition of the same populations. Indeed, individuals that harbor alleles at a locus that can eventually replace each other must be ecologically similar, and there is a reciprocal, mutually reinforcing, relationship between ecological similarity of sympatric individuals and their ability to interbreed. On the one hand, because ecological similarity indirectly causes genetic similarity, genetically similar amphimictic individuals must be compatible to each other and, thus, have no reason not to interbreed. On the other hand, sympatric organisms capable of interbreeding must share recent ancestors and, thus, must be genetically and ecologically similar to each other. Thus, at a particular locus, an allele from any member of the breeding pool may eventually displace all other alleles. In other words, populations *sensu* interbreeding are usually also populations *sensu* lineage survival.

Still, there are exceptions to this rule and, if there is a conflict between the two definitions, it is convenient to define amphimictic populations according to the ability of individuals to interbreed. Two kinds of such exceptions are important. First, two (or more) alleles at a locus can cause their carriers to rely on different resources, leading to indefinite coexistence of these alleles. With apomixis, the carriers of two such alleles would constitute two different populations, such as L and S kinds of *E. coli* (Chapter 1.6). However, the situation is different under amphimixis, because at all other loci expansion and extinction of lineages occurs more or less as usual. In this case, the consequences of ecological differences between alleles at one locus can be best described as polymorphism of this locus maintained by frequency-dependent selection within one population (Section 2.3.2). Here, population *sensu* interbreeding is more inclusive than population *sensu* lineage survival, at least for the locus under frequency-dependent selection.

Second, reproductively isolated individuals may occasionally displace each other due to direct competition, making populations *sensu* interbreeding less inclusive that populations *sensu* lineage survival. For example, American grey squirrel *Sciurus carolinensis*, introduced to Britain in the XIX century, is currently ousting the native red squirrel, *S. vulgaris* (Fig. 2.1.1.2c). From the point of view of persistence of locus-level lineages, squirrels of both species constitute one population in Britain, because the set of all locus-level lineages in red squirrel only is not durable. In contrast, as grey and red squirrels are reproductively isolated in nature, they form two populations *sensu* interbreeding in Britain, and this point of view is more convenient.

Fig. 2.1.1.2c. American grey squirrel *Sciurus carolinensis* (left) that drives European red squirrel *S. vulgaris* (right) to extinction in Britain.

Not all individuals that belong to the same population can compete with each other directly or interbreed. For example, as Darwin discovered in 1854, in many barnacles males are very small, live in obligate association with females, and lack appendages, mouthparts, and digestive, circulatory, and excretory systems (Fig. 2.1.1.2d). Of course, in every species with separate sexes only individuals of the opposite sexes can breed. Still, all members of a population belong to lineages that can interbreed and are ecologically equivalent.

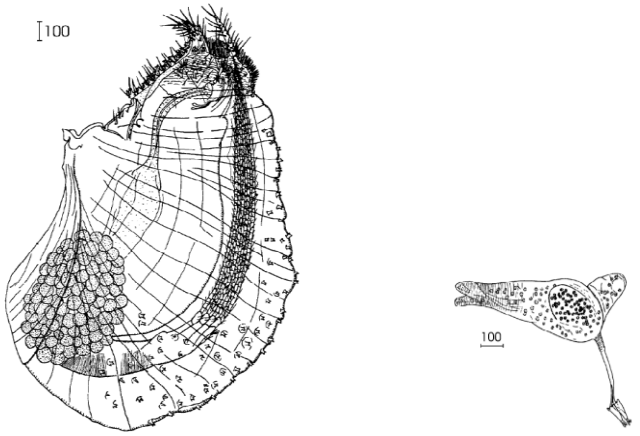

Fig. 2.1.1.2d. Sexual dimorphism in a barnacle *Lithoglyptes bicornis*: female (left) and male (right); scale bars are in μm (*Hydrobiologia* 438, 193, 2000).

One can think that amphimictic populations are more integrated than apomictic populations, because two amphimictic individuals usually share a MRCA in a less remote generation than two apomictic individuals. Indeed, the pedigree of an amphimict contains 2^g ancestors g generations ago (2 parents, 4 grandparents, 2^{20} = 1,048,576 = 1 Megabyte of ancestors 20 generations ago, etc.). When $g > \log_2 N$, this number exceeds the total number of individuals available, so that some ancestors have to appear many times in the genealogy of an individual, resulting in inbreeding. Thus, even within a very large population, two amphimictic individuals usually have multiple common ancestors no more than 30-40 generations ago. However, two amphimicts that share a remote ancestor inherit very little or even no common genes from it. In contrast, under apomixis any common ancestry implies genetic identity, save recent mutations.

To summarize, the need to consider populations comes from the action of the most fundamental evolutionary forces - natural selection, random drift, and amphimixis (Chapter 2.3) and, although amphimixis profoundly affects population-level processes, the notions of apomictic and amphimictic populations are not too different.

2.1.1.3. Why are populations ubiquitous?

We are so used to every individual belonging to a sufficiently large population of similar individuals (Chapter 1.5), that this key property of life, without which Darwinian evolution would be impossible, if often taken for granted. However, the reasons why living beings always form populations are worth considering. Apparently, two such reasons are particularly important.

First, individuals are small as compared to ranges usually available for those who occupy a particular ecological niche. For example, the Ocean can support ~100,000 blue whales, the size of the species before humans begun hunting them - not a whole lot, but still a decent population (Fig. 2.1.1.3a). Thus, because genetic differences cannot accumulate fast, reproduction of even a small number of founders will create many ecologically similar individuals: they will multiply until their number reaches the carrying capacity of the environment.

Fig. 2.1.1.3a. A small habitat that can support only one individual of a particular kind (left) and the range of the blue whales, *Balaenoptera musculus* (right).

Still, this reason is not enough. One can imagine a small island, not unlike the Little Prince's planet, which can support, say, only 10 lions. However, we almost never see such small populations, due to the second reason: a population consisting of too few individuals is doomed. Indeed, random fluctuations of the population size will eventually

cause extinction of a population of just a few individuals. Even more importantly, natural selection cannot prevent accumulation of mildly deleterious mutations in a population of a small size. For example, Florida panther *Puma concolor coryi* was represented, for more than a century, by only ~100 individuals that occupied a restricted range in South Florida and experienced progressively declining fitness Fig. 2.1.1.3b). Introduction of several individuals from Texas reversed this decline, as hybrid kittens reach adulthood with probability almost 3 times higher than purebred Florida kittens, and led to expansion of the Florida panther range.

Fig. 2.1.1.3b. The Florida panther *Puma concolor coryi* (*Anim. Conserv*. 9, 115, 2006).

The minimal long-term viable size of a population is at least ~1000 individuals and may be even higher, perhaps approaching the size of the human population before its recent expansion (Section 2.5.4.5). Individuals of a kind that is not on the brink of extinction must be represented by sizeable populations, where natural selection can operate efficiently, in all or almost all generations. Indeed, due to constant influx of deleterious mutations, efficient selection against them is a necessary condition for the very existence of life (Chapter 2.5).

2.1.1.4. Delimiting populations

So far, we assumed a single, isolated, unstructured population. However, more complex situations are common in nature, and it may be difficult to decide who belongs to a particular population and who does not. Let us consider the rationale for delimiting populations, in the context of studying Microevolution.

In fact, boundaries between local, sympatric populations are usually clear-cut. There are probably at least two factors behind this important generalization. First, under a particular environment, the fitness landscape possesses a finite set of discrete peaks, and

individuals of genotypes that corresponds to a particular peak occupy a distinct ecological niche and form a separate population. Second, reproduction, if amphimictic, provides a positive feedback for similarity: similar enough individuals interbreed, making their offspring even more similar genetically and ecologically, and thus creating well-integrated populations (Fig. 2.1.1.4a). The relative importance of these two factors is not clear, because population structure of ancient, obligate apomicts has not been properly studied. Still, data on bdelloid rotifers demonstrate that apomicts can have populations that are as clear-cut as that of amphimicts.

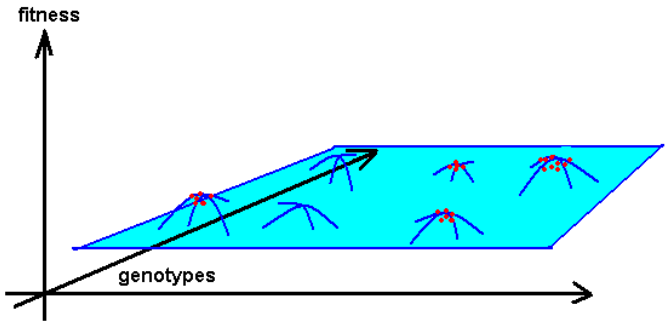

Fig. 2.1.1.4a. Distinct populations, corresponding to some of the isolated fitness peaks.

However, more complex patterns are common when locations of individuals are important, which is the case if we need to consider a wide geographical range, and the typical distance of dispersal of an individual is much shorter than this range. Then, boundaries between populations are often genuinely fuzzy. Should we attribute to the same population two wolfs living in adjacent forests (Fig. 2.1.1.4b)? The answer may depend on what problem we want to consider.

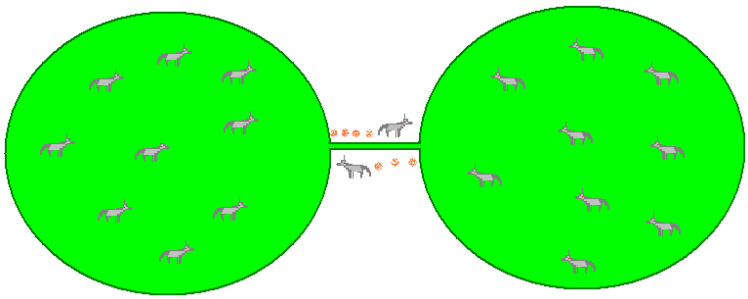

Fig. 2.1.1.4b. Wolves rapidly move within a forest, and every 10 years a wolf migrates from one forest to the other.

Above, our definitions of population were deliberately vague, as they included unspecified "long time". Dealing with different problems, we may be interested in rather different lengths of this "long time", leading to recognition of different populations. Indeed, if we study a short-term process, such as fast, strong selection against substantially deleterious mutations, a small number of generations is sufficient. Then, each forest can be treated as an independent population: in the course of just a few generations the slow influx of wolves from the other forest can be safely ignored, as their alleles will not have a chance to become frequent. In contrast, if we study a long-term process, for example, expansion of a unique advantageous mutation, we need to follow the dynamics of variation for a larger number of generations. Clearly, we cannot consider wolfs from a forest in isolation in this case, because invasion of the advantageous allele from the outside is the essence of this process (Fig 2.1.1.4c; Section 2.3.3). Thus, both forests must be treated as one, spatially-structured population. Finally, if we consider a very slow process, such as random drift (Section 2.3.5), both forests can be viewed as one unstructured population: an allele found after a million of generations in the left forest has almost the same chances of coming from a current wolf from either left or right forest.

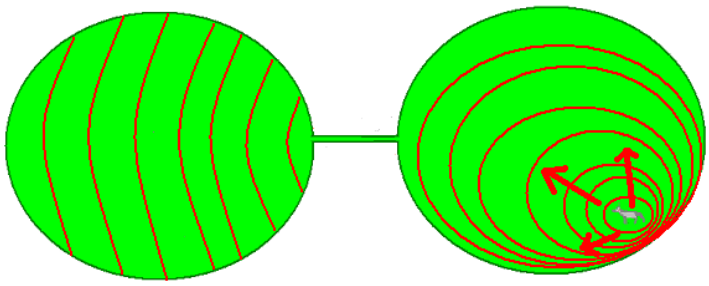

Fig. 2.1.1.4c. Expansion of an advantageous allele that originally emerged in one individual.

Spatial structures of natural populations may be more complex than that shown in Fig. 2.1.1.4b: there may be many partially isolated subpopulations, patches where

individuals can live can appear and disappear, etc. Still, the general rule remains the same: the more long-term a process we wish to study, the more inclusive a population we need to consider (Fig. 2.1.1.4d). The plateau, reached if a very slow process is to be considered, corresponds to the population that includes all individuals that represent allele lineages not protected ecologically against each other, regardless of their current locations.

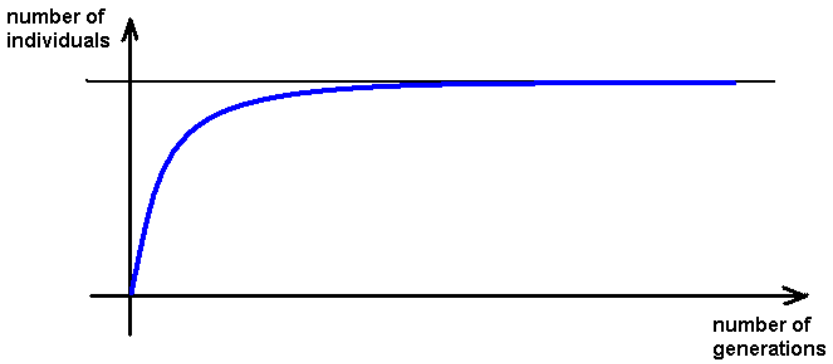

Fig. 2.1.1.4d. The dependence of the number of individuals in the population on the time-scale at which the population is to be considered.

Because our goal is to study Microevolution, we will usually delimit populations inclusively. Indeed, all individuals that inhabit a range such that an advantageous mutation that arose somewhere within this range can reach must be treated as one population (Fig. 2.1.1.4c), as long as we wish to consider the key process of replacement of an old allele with a better, new one. Apparently, amphimixis can make spatially-structured populations more inclusive, as it allows propagation of individual advantageous allele, instead of whole genotypes that may be adapted to local conditions. The most inclusive population, integrated by occasional waves of propagation of advantageous alleles, may encompass the whole species. Indeed, even a limited dispersal is enough for a rapid spread of a gene that enjoys a strong advantage, as it was the case, for example, for P element which rapidly took over the whole species of *Drosophila melanogaster* (Fig. 2.1.1.4e).

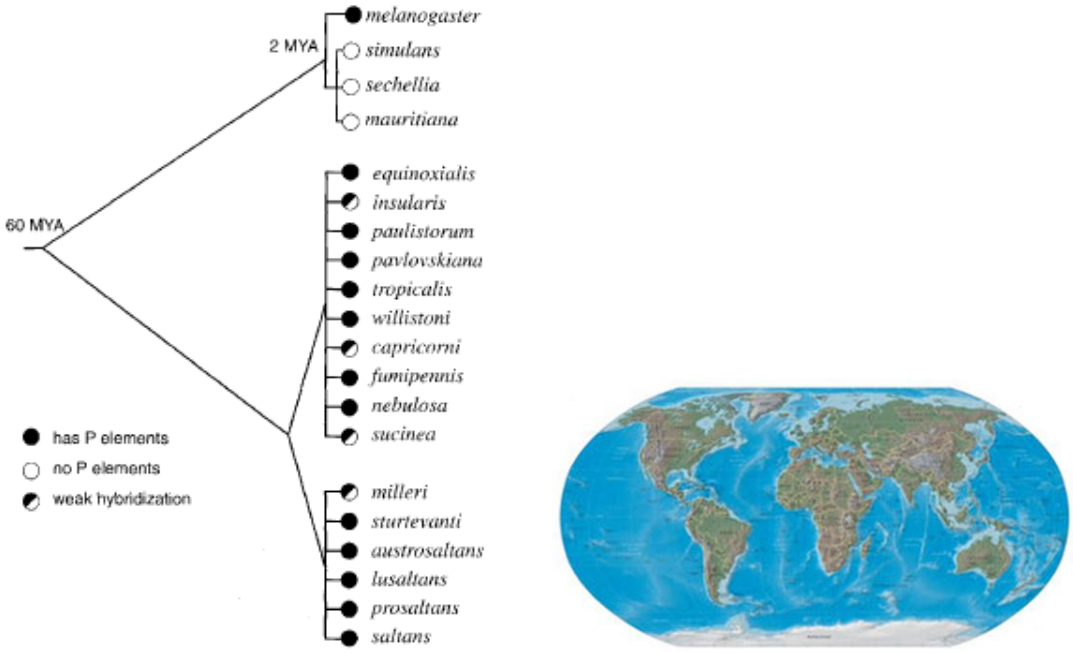

Fig. 2.1.1.4e. P element was acquired by a single *D. melanogaster* individual ~100 years ago somewhere in the New World, where this species has been introduced less that 500 years ago. P element was transferred to *D. melanogaster*, perhaps by a mite's bite, from one of the American species of *Drosophila*, which, in contrast to the closest relatives of *D. melanogaster*, harbor similar transposable elements (left). In early XX century, most of wild-caught *D. melanogaster* were P-negative. Now, however, every *D. melanogaster* throughout its whole global range is P-positive (right), although old laboratory strains remain P-negative. Thus, a single "advantageous" allele took over the whole species in just ~100 years. In fact, P element is deleterious to the host, but enjoys a strong transmission advantage, because it takes just one infected parent to infect all the offspring (*Bioessays* 14, 681, 1992).

Still, a species may consist of completely isolated populations, if dispersal between different parts of its range ceased altogether at some moment (Fig. 2.1.1.4f). Ancestors of Native Americans that reached the New World ~14,000 years ago (Section 1.4.2.5) constituted a separate population for a long time, after the Bering Bridge disappeared, but always remained *Homo sapiens*. Eventually, completely isolated populations will diverge into different species (Section 2.6.2), but this can take a very long time.

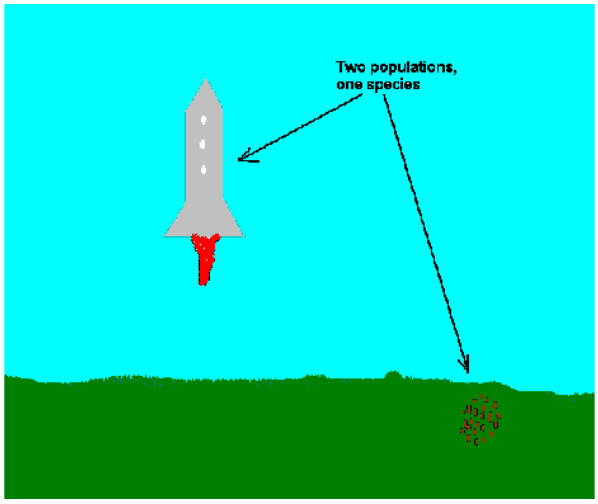

Fig. 2.1.1.4f. The crew of a spaceship, bound to another galaxy, will become a separate population right after the take-off, but will remain *Homo sapiens* for many thousands of generations.

Complications of another kind arise when genetic exchanges between individuals occur not in the course of regular amphimixis, but due to LGT, often from rather dissimilar donors (Chapter 1.5). At a short time-scale, LGT can be ignored. However, on a very long time scale, even rare LGT can, for evolutionary purposes, effectively make one population from a wide variety of diverse bacteria.

2.1.1.5. Population biology and evolution

Populational level of organization of life has its unique features, which affects how Microevolution is studied. Most importantly, populations consist of individuals, instead of organisms, in the sense that properties of populations do not depend on what is inside the organisms (Fig. 2.1.1.5a). "External" traits that determine how an individual acts as a member of the population, such as fitness, mutation rate, mate choice, or the probability of dispersal matter, but "internal" traits, such as body size of the number of vertebrae do not. If we know that allele A has a 1% fitness advantage over allele a, this is all what is needed to determine how A will replace a, and we do not care whether A makes horns longer, or leaves greener, or brains smarter. Thus, populations are, in a sense, much simpler than constituent organisms. There is nothing unique about this: the

structure of a University (President, Provost, Colleges, Departments, ...) is also simpler than human anatomy.

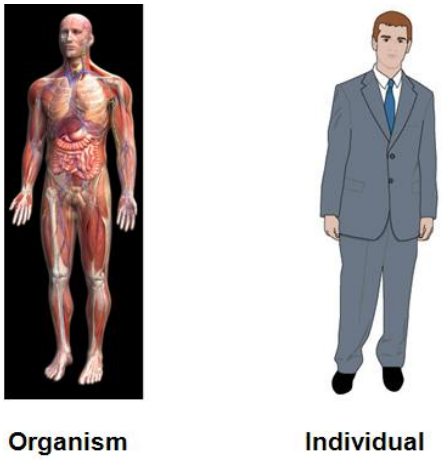

Fig. 2.1.1.5a. Organisms and individuals.

Thus, although natural selection acts upon within-population genetic variation, population-level analyses are usually unsuitable to study the fitness landscape. Instead, the fitness landscape must be somehow known before theory of Microevolution can be applied to a particular population. The only exception is when the fitness is determined by population-level factors, for example, when the evolution of mutation or recombination rate is studied (Chapter 3.3). Thus, the most important issues in evolutionary biology, concerned with the evolution of complex, functioning phenotypes that describe internal working of organisms (Chapter 3.2) cannot be addressed at the population level. Population-level analysis cannot shed any light on the evolution of human eye. Still, such analyses, due to their relative simplicity, are very successful within their domain, as we will see later in this Part and in Chapters 3.1 and 3.3. Because only genes are transmitted between generations, and fitness is the only phenotypic trait that matters for selection, we can study Microevolution of genotypes separately, and then add phenotypic implications to it, by taking into account genotype > phenotype maps. In contrast, purely phenotypical approaches to Microevolution do not work.

Biology at the population level is subdivided into population ecology and population genetics. To some extent, this subdivision reflects the nature of things. On the one hand, changes of population sizes, studied by population ecology, may be

approximately independent of changes of the genetic composition of populations. On the other hand, evolution of the genetic composition of a population can be studied, in simplest situations, ignoring the dynamics of the population size (Section 2.1.4). Naturally, we will concentrate on population genetics, because genetic changes constitute evolution. Still, in many cases ecological and genetical changes of populations have to be considered together (Chapter 3.4).

When compared to a molecule or a cell, which are small and can change very fast, a population may seem to be an easy object for experimental investigation. However, this is not the case. Natural populations are so large and loose and their changes are so slow that some of their basic properties remain poorly known (Chapters 2.2 and 2.5).

Natural populations present a staggering variety of sizes, spatial structures, levels of genetic variation, and other features. Absolute sizes of inclusive populations of multicellular organisms vary between ~10^3 to perhaps ~10^{15}, and populations of prokaryotes and protists can be even more numerous. A population size can be approximately constant, increase, decline, or fluctuate. Ranges of populations vary from a small remote island to the whole Wold Ocean. The range of a population can be constant, expand due to invasions into new areas, shrink due to local extinctions, or split into parts. The level of genetic variation, characterized by the fraction of differences between two randomly chosen genotypes from the same population, can vary between ~0.001 (as in *Homo sapiens*) to ~0.1 (as in *Ciona savignyi*). These data will be treated in detail later.

Section 2.1.2. Populations on fitness landscapes

Due to paramount importance of natural selection, theory of Microevolution is based on the concept of fitness landscape. Since the range of within-population variation is narrow, Microevolution depends primarily on small-scale features of fitness landscapes. If similar genotypes have similar fitnesses, at a small scale any fitness landscape can be approximated by a hyperplane, and the fitness of a genotype is determined by just one variable, called fitness potential. Planar fitness landscapes are called non-epistatic. However, epistasis, *i. e*. deviations from planarity, due to non-independent contributions of different loci into fitness, is also important even at the scale of within-population variation. Two different, and not mutually exclusive, forms of

epistasis are multidimensional and sign epistasis. Natural selection is defined both by the fitness landscape and by how the population is located on it. Selection can be negative or positive; directional, stabilizing, or disruptive; narrowing or widening; incompatibility or complementation; hard or soft; constant or frequency-dependent; and real or apparent.

2.1.2.1. Linear fitness landscapes and fitness potential

The key concept of fitness landscape was already used as the conceptual basis for several kinds of indirect evidence for past evolution (Section 1.1.1). If the complete genotypes (or phenotypes) are considered, fitness landscape is a graph of an incredibly complex function which relates a genotype, described by very many variables, to its fitness. Under any particular environment, such a landscape probably has multiple peaks, although fitness is zero for a vast majority of possible genotypes. However, at any particular moment, the course of Microevolution depends only on a tiny portion of the fitness landscape, covered by the spot, within the space of genotypes, that corresponds to genotypes that are currently present within the population. So, how does a fitness landscape look under microscope?

Let us assume that, at the scale of within-population variation, fitness is a smooth function of the genotype, so that a small change of the genotype leads to only a small change in fitness. In other words, we assume that genotypes that are adjacent to each other in the space of genotypes, in the sense that they can be transformed into each other by a small number of simple changes, have similar fitnesses. If so, a mathematical fact is that locally, under a strong enough magnification, any fitness landscape is close to linear, *i. e*., can be approximated by a hyperplane flying over the space of genotypes (Fig. 2.1.2.1a). Although we cannot draw fitness landscapes over phase spaces of more than 3 dimensions, situation remains the same for any number of dimensions.

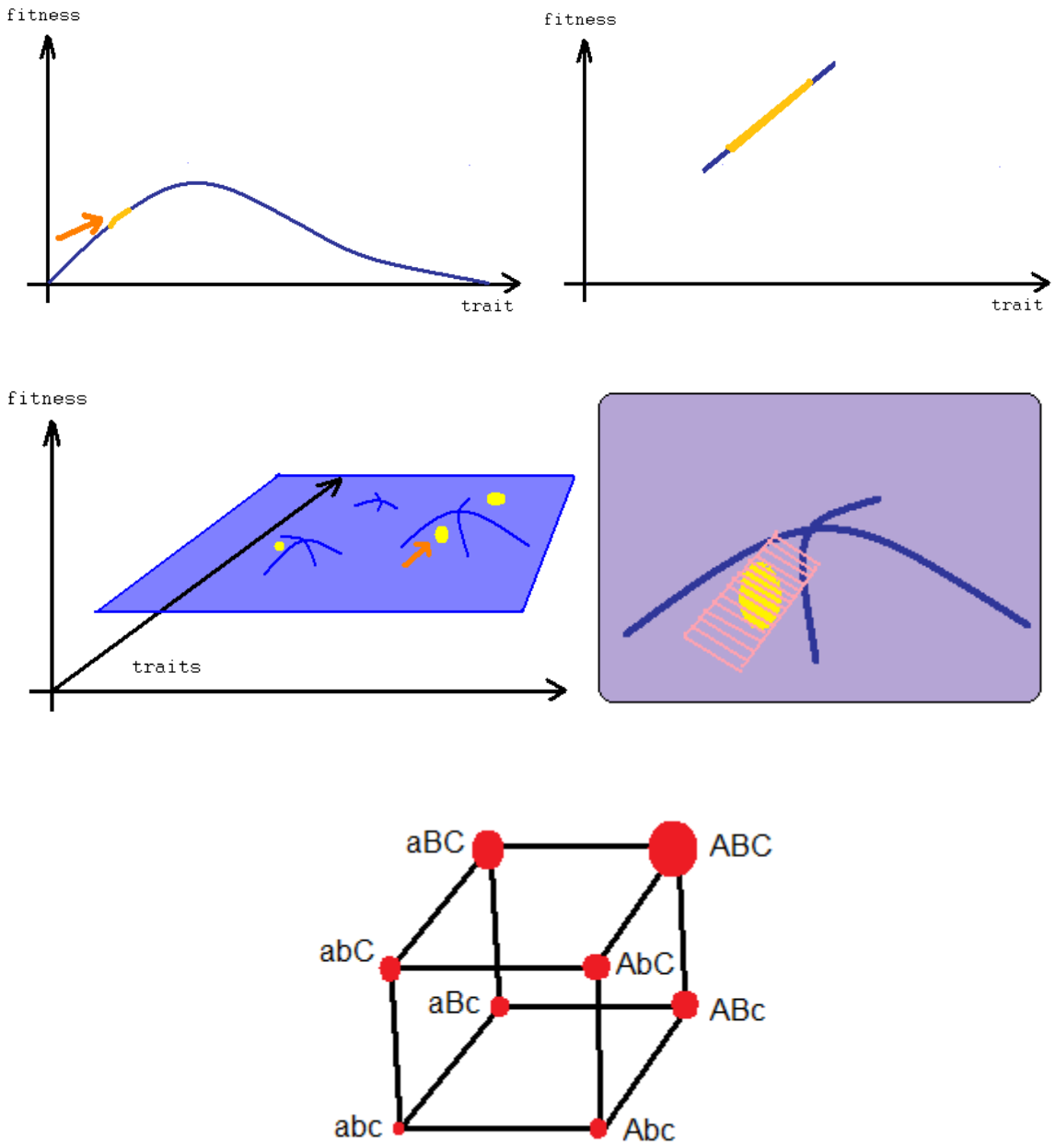

Fig. 2.1.2.1a. At the small scale of within-population variation, any smooth fitness landscape is close to a plane within the space of genotypes or phenotypes. (top) Fitness landscape over 1-dimensional phase space that corresponds to one quantitative trait, with the range of within-population variation shown by yellow line (orange arrow) (left), and its corresponding portion, close to a straight line, under magnification (right). (middle) The analogous situation in the 2-dimensional space of two quantitative traits with the fitness landscape from Fig I33. (bottom). Fitness landscape over a 3-dimensional space of

genotypes at three diallelic loci, A, B, and C, with upper case-letter alleles increasing fitness. Here, due to too many dimensions, fitness is shown by the size of a red ball.

Regardless of the number of dimensions in the phase space, an (approximately) linear fitness landscape has two key properties. First, the fitness of a genotype can be represented by the sum of constant contributions from all its constituent allele. Second, there is just one direction, known as gradient, in which fitness changes. Thus, the fitness of a genotype is determined by its position alone the axis that points in the direction of gradient. This position is called the fitness potential of the genotype, because it alone determines its fitness. Indeed, if a genotype changes in any direction that is perpendicular to the gradient, its fitness is not affected (Fig. 2.1.2.1b).

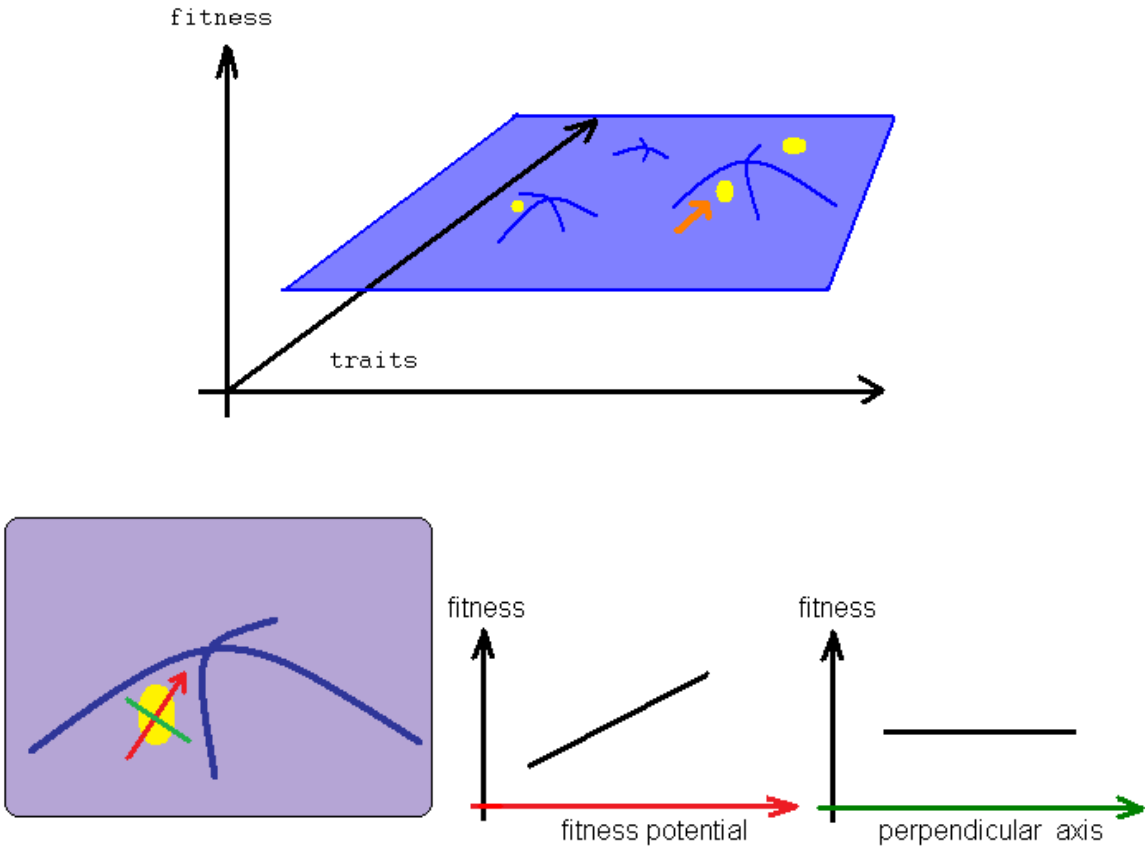

Fig. 2.1.2.1b. The same two-dimensional fitness landscape as in Fig. 2.1.2.1a, at the scale of within-population variation. Fitness potential axis is shown in red, and the only (because there are only 2 dimensions here) perpendicular axis is in green. Fitness is an

approximately linear function of the fitness potential of a genotype within the population and does not depend on its position along the perpendicular axis.

Thus, as a first approximation, fitness at a small scale depends on just one quantitative trait. All the within-population variation contributes to variation of fitness potential, with small invariant contributions of different alleles being independent, after which fitness potential determines fitness. The fitness potential of a complete genotype may be thought of as the sum of contributions of its advantageous alleles minus the sum of contributions of its deleterious alleles.

The key assumption of the above analysis if that fitness changes smoothly. In reality, fitnesses of even the closest genotypes can be very different: replacing just one nucleotide can kill even the most fit individual. Still, variants causing such drastic reduction of fitness do not play an important role in variation of natural populations, and variants which dramatically increase fitness are extremely rare, since most of natural genotypes already have high enough fitnesses, unless the environment had just changed drastically. Thus, fitness as a linear function of a single variable, fitness potential, is the proper point of departure for consideration of natural selection.

2.1.2.2. Epistasis

Still, even on the scale of within-population variation, fitness landscape as a linear function of fitness potential is not always a sufficient approximation. For reasons which will become clear later, we will mostly consider fitness on the logarithmic scale, *i. e*. log fitness will be our dependent variable. Of course, the above analysis was equally applicable to fitness and log fitness. The simplest example of a deviation of log fitness from linearity is dominance. If we consider just one locus (partial genotype) A, with wild-type allele A and mutant allele a, the log fitness of heterozygote Aa may be closer to the log fitness of AA (if A is dominant) or to the log fitness of aa (if A is recessive), or be the arithmetic mean of the log fitnesses of AA and aa (intermediate dominance, Fig. 2.1.2.2a). Here, the assumption that fitness depends on just one variable, fitness potential (the number of alleles a in the genotype) is still valid, as long as we ignore other loci and assume that heterozygotes Aa and aA has the same fitness, but log fitness is a linear function of this fitness potential only if A is exactly intermediately dominant. If alleles A

and a are not too different, intermediate dominance is probably the rule, but for alleles with large effects deviations from linearity are the norm.

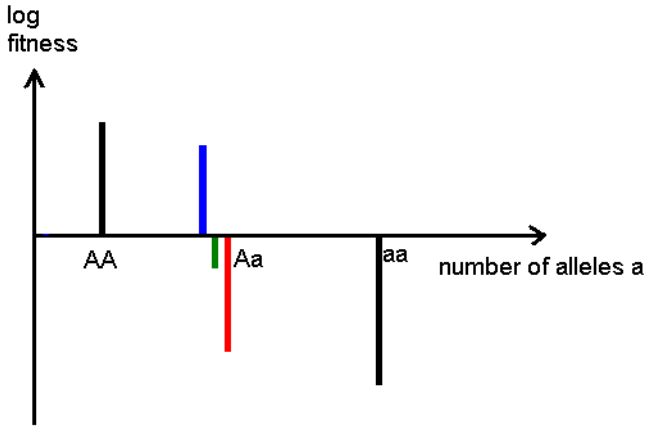

Fig. 2.1.2.2a. Dominance of the wild-type allele A (blue), intermediate dominance (green), and dominance of low-fitness allele a (red).

Thus, we need to consider fitness landscapes more complex than graphs of linear functions of fitness potential. **Any deviation of a fitness landscape from log linearity is called epistasis**. Genetically, such deviations correspond to deviations from additivity of fixed contributions of different alleles into log fitness.

Generic epistasis simply means that we can have an arbitrary fitness landscape, with multiple peaks, minima, etc. (Fig. 2.1.2.1b). Such landscapes are necessary for consideration of Macroevolution (Chapter 3.2). However, within a simpler context of Microevolution, it makes sense to consider two intermediate kinds of epistasis, which generalize simple linearity but are still more restrictive than the generic case. Indeed, it is unlikely that, for example, many fitness peaks fall within the range of within-population variation.

The first restrictive kind of epistasis is one-dimensional epistasis. It inherits, from the simplest linear case, the assumption that there is just one fitness-determining variable, fitness potential. However, now fitness can be an arbitrary function of this variable (Fig. 2.1.2.2b).

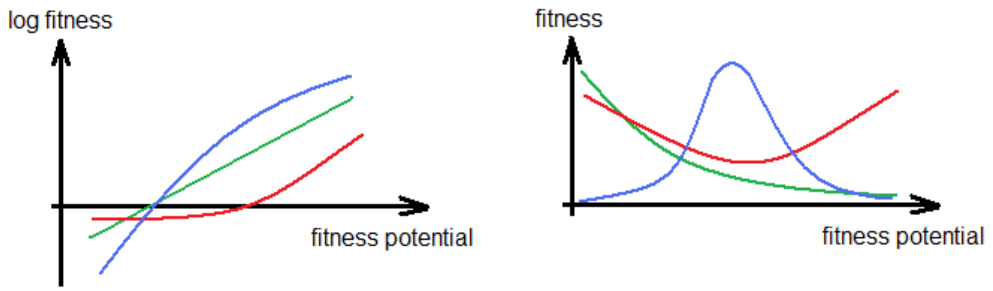

Fig. 2.1.2.2b. Examples of one-dimensional epistasis. (left) Log fitness is plotted; no epistasis (green), convex (blue), and concave (red) fitness functions. (right) Fitness is plotted; no epistasis (green), unimodal (blue), and bimodal (red) fitness functions.

Mathematically, even a small, generic deviation from linearity does not fit into the framework of one-dimensional epistasis, because a deviating fitness landscapes will not remain level in the directions perpendicular to the former fitness potential. Still, one-dimensional epistasis is a commonly used model with intuitive appeal and some empirical support, at within-population scale. It is flexible enough, and yet more tractable than the generic case. Modes of epistasis that do not fit into the one-dimensional framework are collectively called multidimensional epistasis.

The second restrictive kind of epistasis can be called monotonic, meaning that a particular genetic change never impacts fitness in the opposite directions. Modes of epistasis that do not fit into this framework are collectively called sign epistasis. The two restrictive modes of epistasis are not equivalent: one-dimensional epistasis can be sign epistasis and monotonic epistasis can be multidimensional (Fig. 2.1.2.2c).

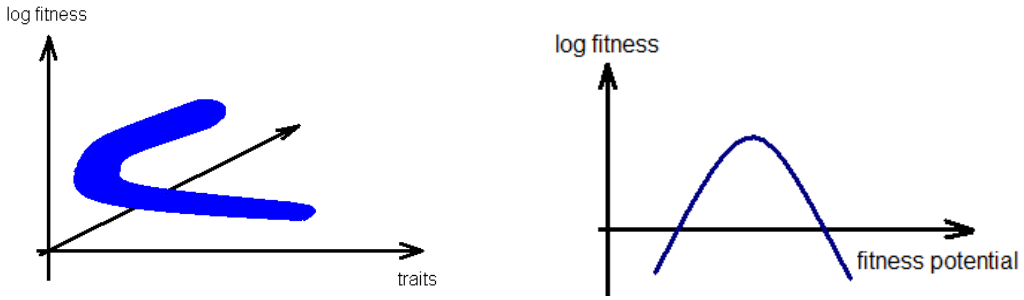

Fig. 2.1.2.2c. (left) Monotonic, multidimensional epistais: high values of both traits are deleterious, and these deleterious effect reinforce each other. (right) Sign, one-dimensional epistasis: intermediate values of the trait confer the highest fitness.

Fitness landscapes are behind any evolution by natural selection, and the concept of epistasis provides the framework for understanding them. Unfortunately, because a population is just a tiny spot in the space of genotypes, it illuminates only a tiny spot on the global fitness landscape, and thus reveals only its local properties, insufficient to understand Macroevolution. Thus, global properties of fitness landscapes are still known rather poorly (Chapter 3.2).

2.1.2.3. Modes of selection

The concept of epistasis is applicable to even empty fitness landscapes, considered regardless of the presence of any individuals. In contrast, natural selection is determined both by the fitness landscape under the current environment and by the distribution of within-population variation. Populations which are located differently on the same fitness landscape can experience very different kinds of selection (Fig. 2.1.2.3a). Thus, in order to obtain a useful classification of possible modes of natural selection, we need to relate fitness landscapes to patterns in within-population variation.

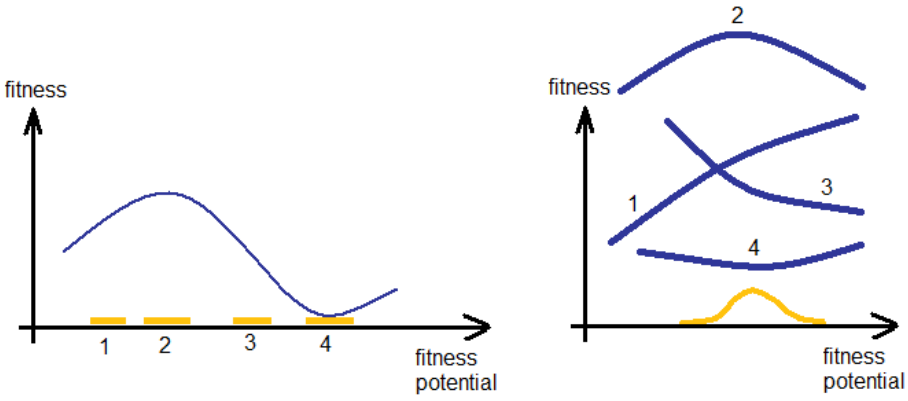

Fig. 2.1.2.3a. Selection favors high, intermediate, low, and extreme values of the trait in populations 1, 2, 3, and 4, respectively.

Let us start from the simplest case of unordered genotypes. Then, just two key modes of selection are possible, which do not depend on subtle features of the fitness landscape (Fig. 2.1.2.3b):

i) Negative selection - the most fit of the available genotypes is common in the population, and less fit genotypes are rare,

ii) Positive selection - the most fit of the available genotypes is rare, and the most common genotype is less fit.

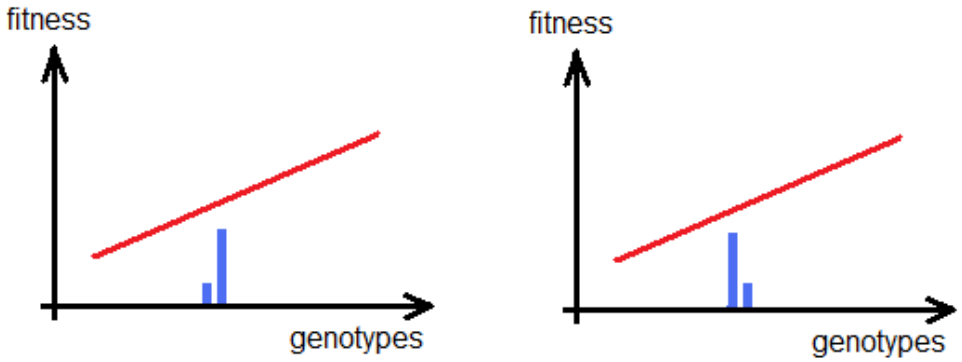

Fig. 2.1.2.3b. The same fitness landscape (red line) induces negative selection in a population with just two genotypes if the common genotype is superior (left) and positive selection if it is inferior (right).

Obviously, the impact of negative selection, the most common mode of natural selection (Chapter 1.5) is to maintain the *status quo*, by eliminating rare inferior genotypes that are constantly introduced by mutation and/or immigration. In contrast, the impact of positive selection is to promote changes, by driving initially rare genotypes towards fixation, and to lead to adaptive evolution.

Let us now consider genotypes arranged by their values of a quantitative trait, which can be a genotype-level trait such as fitness potential or a phenotypic trait such as body size. Then, two new perspectives on selection must be considered. First, we can classify selection (Fig. 2.1.2.2b right and Fig. 2.1.2.3a right) into:

i) directional: fitness increases or decreases monotonously, favoring genotypes with one of rare extreme values of the trait,

ii) stabilizing: fitness has one maximum, favoring genotypes possessing intermediate, common values of the trait, and

iii) disruptive: fitness has two maxima, favoring genotypes with either of the two extreme values of the trait.

More complex forms of selection, with multiple maxima and minima on the fitness landscape within the range of within-population variation are probably uncommon. Roughly speaking, stabilizing selection can be regarded as negative, and directional and disruptive selection as positive.

The second, and to some extent related perspective is to classify selection by its impact on the variance of the quantitative trait it acts upon. A useful classification exists only if we assume that the trait has Gaussian distribution (Section 2.1.3). Then, selection is narrowing, reducing the variance, if log fitness is concave (its second derivative is negative everywhere) and is widening, increasing the variance, if log fitness is always convex (positive second derivative) (Fig. 2.1.2.2b, left). When the log fitness is linear, so that fitness is exponential, the variance of the Gaussian trait does not change. As it was the case with the previous classification, more complex situations, when selection is neither narrowing nor widening are possible, but perhaps not common. Obviously, stabilizing selection is narrowing and disruptive is widening, and directional selection can both increase and decrease the variance of the trait.

Because fitness cannot increase indefinitely, narrowing selection is biologically realistic. In particular, we expect to encounter it on the slopes of a fitness peak. Still, widening selection may operate in a population located close to fitness minimum, which may be possible under some circumstances (Chaper 2.6). Interpretation of narrowing selection depends on its direction. If the trait under selection is the number of advantageous alleles (so that fitness is an increasing function of this trait), narrowing selection can be viewed as a case of diminishing returns: each next beneficial allele leads to a smaller increase in log fitness. In contrast, if the trait is the number of deleterious alleles, so that fitness decreases with it, narrowing selection is a case of synergism: each next deleterious allele causes a larger decline of log fitness (Fig. 2.1.2.3c). Widening selection obviously results in the opposite pattern.

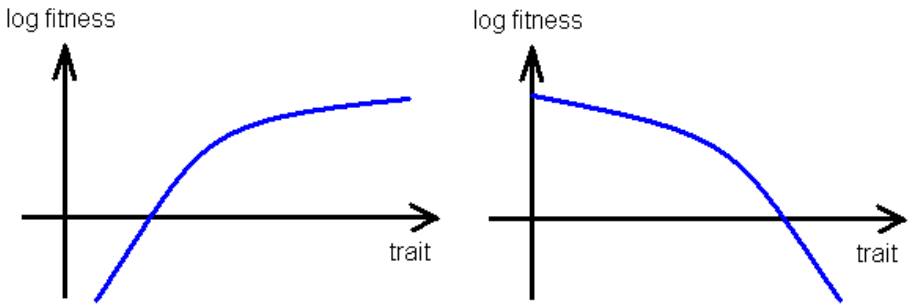

Fig. 2.1.2.3c. Narrowing selection with increasing fitness leads to diminishing returns (left), and narrowing selection with decreasing fitness leads to synergism (right).

Let us now consider the second special kind of non-linear fitness landscapes, those that are monotonous but not necessarily one-dimensional. Two opposite kinds of selection are possible with such landscapes, incompatibility and complementation selection (Fig. 2.1.2.3d). Incompatibility selection can lead to speciation (Chapter 2.6).

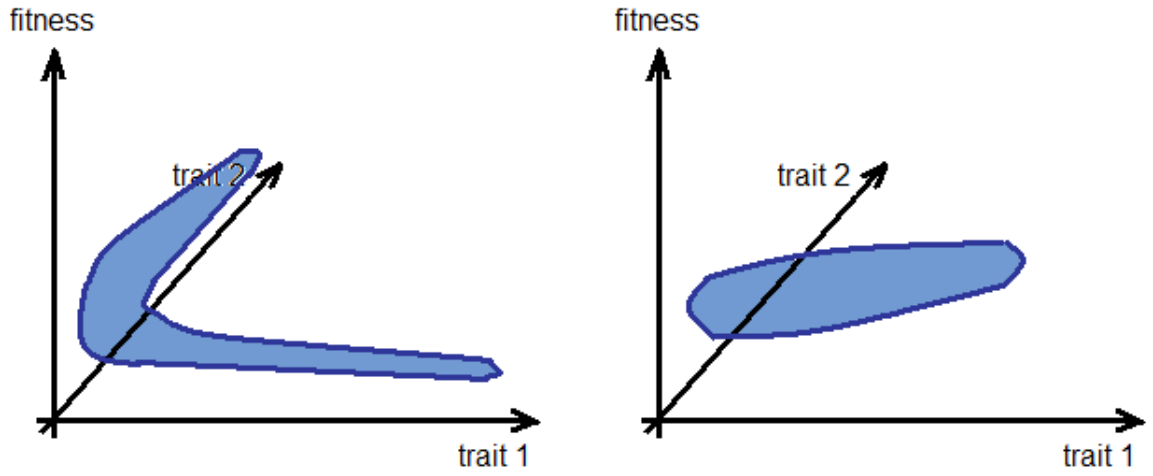

Fig. 2.1.2.3d. (left) Incompatibility selection: high values of the two traits reinforce negative impacts of each other. (right) Complementation selection: high values of the two traits mitigate negative impacts of each other.

Even if we stay within the range of within-population variation, it is hard to obtain real data which can substantiate the nice pictures presented in this Subsection. Because neither genotypes nor fitnesses of individuals are easy to measure, quantities like the second derivative of log fitness as the function of fitness potential are almost impossible

to ascertain directly, although some indirect inferences can help. In fact, revealing real small-scale features of fitness landscapes and modes of selection is the main challenge facing experimental studies of Microevolution (Sections 2.3.2 and 2.4.4). Still, the approach outlined above provides the correct framework for asking questions about natural selection.

2.1.2.4. Population-dependent fitness landscapes

So far, we assumed that the fitness landscape does not depend on the state of the population in which selection operates. This may be the case if selection is due to abiotic factors (*e. g.*, temperature) or if we consider only the contribution into fitness by a partial genotype or phenotype. In fact, only the invariance of relative fitnesses matters: if under some conditions (*e. g.*, when the population size changes) the absolute fitness of each genotype is multiplied by the same positive number, the process of selection is not affected.

However, natural selection is often mediated by intrapopulation interactions, in particular, by competition (Section 2.3.2). Then, even relative fitnesses can depend on the population state. Two kinds of dependencies of selection on the state of the population are of particular conceptual importance.

First, intrapopulation interactions can affect directional selection. Let as consider one-dimensional epistasis and assume that fitness of a genotype depends on the fraction of the population that has the fitness potential below that of the genotype. For example, selection can be due to a fight with an opponent, chosen randomly, and an individual wins if its opponent is weaker. In this situation, the fitness of a genotype is determined by its relative position within the range of within-population variation. Such selection is called soft, as opposed to invariant hard selection (Fig. 2.1.2.4a).

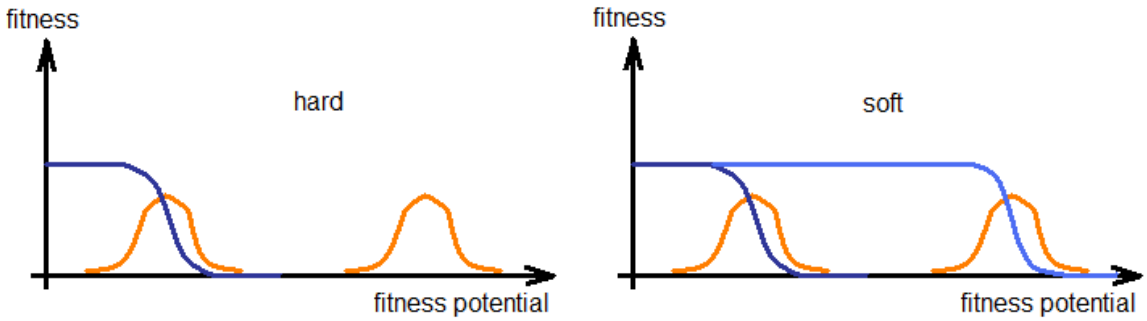

Fig. 2.1.2.4a. Under hard selection (left), fitness landscape does not depend on the distribution of the fitness potential within the population, and under soft selection fitness landscape is determined by this distribution (right).

Second, even the direction of selection can depend on the state of the population. Such selection is called frequency-dependent. It is natural to assume that, if different organisms utilize different resources, those with rare genotypes and/or phenotypes will have an increased relative fitness due to reduced competition. Such frequency-dependent selection is called balancing, since it protects genetic variation (Section 2.4.2) and the opposite mode of frequency-dependent selection, favoring the common genotype, may be called unbalancing.

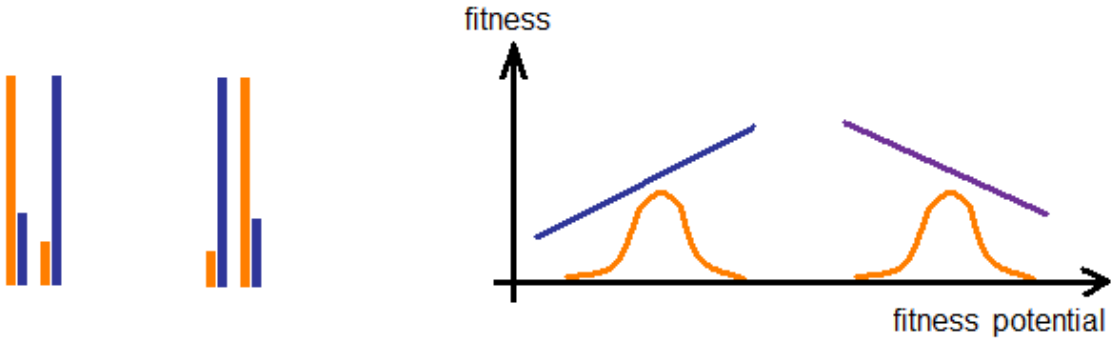

Fig. 2.1.2.4b. Frequency-dependent selection in the case of two genotypes (left) and a quantitative trait (right).

Absolute fitnesses must depend on population density in order to prevent unlimited growth or decline of the population size. However, even relative fitnesses may depend on it, in which case we are dealing with density-dependent selection. In the

extreme case, some genotypes can be advantageous when density is high (tolerant) and some when it is low (aggressive), which can lead to complex dynamics.

In general, the whole fitness landscape is an arbitrary function within the space of population compositions (Section 2.1.3), which can lead to intractably complex situations. However, in the extreme case of a very limited within-population variation, we may assume that at each moment only two genotypes are present, a common ("resident") and a rare ("invader"), and that fitness landscape is determined by this pair. This and other approaches can be used to study complex dependencies of selection on the state of the population, which is necessary to study Macroevolution of simple phenotypes of individuals (Chapter 3.3).

2.1.2.5. Real and apparent selection

We do not have complete data on either fitness landscapes or within-population variation. In particular, only partial genotypes and/or phenotypes of individuals are usually assayed. Thus, when differences in fitnesses between (partial) genotypes or phenotypes are observed, we need to determine whether selection acting on what we observe is real or apparent. Indeed, the trait we study may either affect fitness directly or, alternatively, may be selectively neutral itself, with the appearance of selection on it caused by its association with some other, hidden, trait(s) which actually affects fitness.

Apparent selection can be due to non-independent distributions of different traits. Consider, as an example, a locus (nucleotide site) 1, with two alleles (nucleotides) present in the population, A and G. Suppose that measurements of fitness in a large sample of (haploid) individuals, indicate that those carrying G at this site leave on average 1% more offspring than those carrying A. This difference can be either due to the direct effect of locus 1 on fitness, or due to its association, within the population, with some other, selectively important locus 2, in which case 1 *per se* may have no effect on fitness (Fig. 2.1.2.5a). Such an explanation is very plausible if locus 1 appears to be not very functionally important, for example, corresponds to a synonymous coding site. Of course, if alleles at a locus are distributed independently of the rest of the genetic variation within the population, genotype-level apparent selection at this locus is impossible.

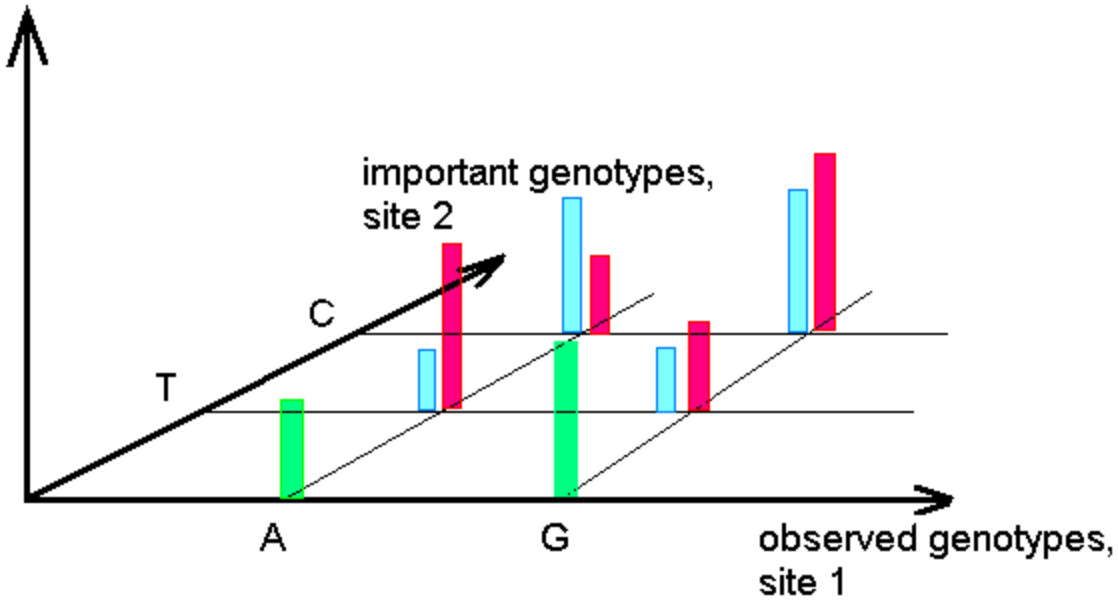

Fig. 2.1.2.5a. Apparent selection at locus 1, due to its association with locus 2, which is under real selection. Allele A at locus 1 preferentially occurs, within the studied population, with allele T at locus 2, and allele G at locus 1 is associated with allele C at locus 2. C confers fitness that is 2% higher than fitness conferred by T, and locus 1 does not affect fitness at all. Green bars - apparent fitnesses of A and G, blue bars - real fitnesses of the four genotypes, pink bars - their frequencies.

Apparent selection can also appear at the level of phenotypes, due to pleiotropy, without any correlated distributions of alleles at different loci. Consider a phenotypic quantitative trait, *e. g.*, body size, with just three values - 1, 2, and 3. Suppose that we observe that individuals with intermediate body size 2 possess, on average, a higher fitness than those with body sizes 1 or 3. This, of course, could be because stabilizing selection directly acts on body size. However, body size could also be selectively neutral, if individuals of intermediate body size possess some other features which are favored by selection. Let us assume that the population is polymorphic at two loci, I and II, each with a common beneficial allele (I+ and II+) and a rarer deleterious allele (I- and II-). Allele I- increases body size, and allele II- decreases it by the same amount. Thus, individuals with small body size have genotype I+II-, individuals with large body size have genotype I-II+, and individuals with intermediate body size can have either of the

two genotypes, I+II+ and I-II-. Then, if selection acts only on the number of beneficial alleles (0, 1, or 2 in the haploid genome), fitness of individuals with intermediate body size will be the highest, assuming that deleterious alleles are rare, because intermediate-size individuals possess the lowest average number of deleterious alleles (Fig. 2.1.2.5b). Thus, there will be apparent selection will act on the body size. The problem of real vs. apparent selection is still far from being resolved: we do not know to what extent selection acting on easily measurable phenotypic traits, such as body size, is real (Chapters 2.2 and 2.5).

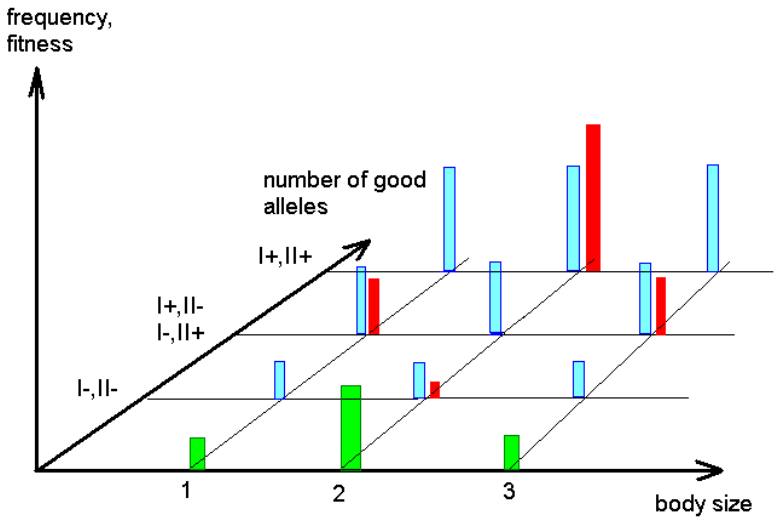

Fig. 2.1.2.5b. Individuals with average body size possess, on average, a smaller number of deleterious alleles that those with extreme body sizes, leading to apparent selection.

Section 2.1.3. Describing and assaying within-population variation

All populations are genetically and phenotypically variable. Three kinds of traits, structureless, characterized by their entropy or virtual heterozygosity; quantitative, characterized by their mean, variance, and higher moments; and complex, can be used to describe variation. Genetic variation within a population can be naturally partitioned into distinct variable traits, mostly single-nucleotide substitutions and simple insertions and deletions. It may be possible to consider only a part of the genome, as long as selection affects this part independently of the rest of the genome. The full description of genetic

variation requires knowledge of frequencies of all genotypes, but, fortunately, simplified descriptions are often sufficient. Microevolution can be viewed as movement of the population within the space of all its possible compositions. Any investigation of a natural population is based on gathering data on some constituent individuals. Usually, only a sample of individuals from the population is studied, and parameters of the whole population, together with their sampling errors, are inferred from the data on the sample.

2.1.3.1. Structureless traits

Individuals within a population differ from each other in both their genotypes and phenotypes, and this variation may be partitioned into traits. Let us first consider simple traits that possess no structure: two states of such a trait can be either identical or different, without any order or other relationship between different states. Any trait with only two possible states, such as locus with two alleles, belongs to this kind. However, multistate traits can also be structureless, as it is the case for a site (1-nucleotide locus) that can be occupied by any of the four nucleotides, A, T, G, and C.

Obviously, variation of a structureless trait A with I states A_1, ... A_I, is fully described by $[A_i]$ (i = 1, ..., I), the frequency of the i-th state of the trait (any I-1 of them are sufficient, because $\sum_{i=1}^{I}[A_i]=1$). The overall level of such variation can be characterized by a single number in a variety of ways. Mathematically, the best characteristic is Shannon's entropy:

$$E=-\sum_{i=1}^{I}[A_i]\log_2[A_i] \qquad (2.1.3.1\text{-}1)$$

where $[A_i]\log_2[A_i]$ is defined as 0 when $[A_i] = 0$. It is easy to see that E = 0 when there is no variation ($[A_i] = 1$ for one value of i, and $[A_i] = 0$ for all other values of i), and E is maximal, for a trait with I states, when all the I states are equally frequent.

However, entropy is not commonly used in population studies, and another measure, called virtual heterozygosity, is more popular:

$$H = 1 - \sum_{i=1}^{I} [\mathrm{Ai}]^2 \qquad (2.1.3.1\text{-}2)$$

Virtual heterozygosity is equal to the fraction of heterozygotes in a diploid population with allele frequencies $[A_i]$, where zygotes were formed by random union of gametes. In other words, H is the probability that two alleles, randomly chosen from the population, differ from each other. Of course, H can be calculated for all kinds of populations, apomictic and amphimictic, and for all kinds of traits. Analogously to entropy, H = 0 if and only if the population is not variable, and reaches maximum, 1/I, when all the I states are equally frequent. When applied to sequence-level data, H is known as nucleotide diversity π.

Often, we need to consider simultaneously several variable, structureless traits. Joint distribution of two structureless traits A and B is described simply by the frequencies of individuals carrying each possible combination of their states, $[A_iB_j]$. Two traits are distributed independently within the population if $[A_iB_j] = [A_i][B_j]$. If this is not the case, a key question is: how are these two traits associated with each other? Let us consider the simplest case of two traits (loci), each with two states (alleles), A_1 and A_2, and B_1 and B_2. Association between them can be characterized by the coefficient of association $D_{A,B}$:

$$D_{A,B} = [A_1B_1]\,[A_2B_2] - [A_1B_2]\,[A_2B_1] \qquad (2.1.3.1\text{-}3)$$

If traits A and B are distributed independently of each other, $D_{A,B} = [A_1][B_1][A_2][B_2] - [A_1][B_2][A_2][B_1] = 0$. Under given allele frequencies at the two loci $[A_1]$ and $[B_1]$, D deviates from 0 maximally no more than three genotypes are present in the population, and one is completely absent. In other words, association between loci is maximal, where their joint distribution is hierarchical (Section 1.1.1.6): knowing what a genotype possesses at one locus carries maximal information about the other locus, if at least one genotype is absent in the population. In a special case when $[A_1] = [B_1]$ (or $[A_1] = [B_2]$), $D_{A,B}$ deviates from 0 maximally, being $D_{A,B} = [A_1]^2$ (or $D_{A,B} = -[A_1]^2$) if this hierarchy is poor, *i. e.*, if A_1 always occurs together with B_1 (or with B_2), which is makes it possible

to exactly infer the allele at one locus from knowing the allele at the other locus, within the same genotype.

The concept of D can be easily generalized to an arbitrary number of states of each of the two traits. Moreover, we can consider higher-order associations between multiple structureless traits. For M traits, there are $\binom{M}{2}$ pairwise associations, $\binom{M}{3}$ 3-way associations, and 1 M-way association. The corresponding theory is a rather straightforward generalization of the coefficient of pairwise association D.

2.1.3.2. Quantitative and complex traits

The next simplest kind of traits are quantitative traits. Each state of such a trait is characterized by a number, so that the states are ordered and some pairs of different states are closer to each other than other pairs. A quantitative trait, as well as a structureless trait, can describe both genotypes and phenotypes of individuals, for example, the number of deleterious alleles or a body mass. Below, expressions for a continuous quantitative trait x are presented, but the corresponding expressions for a discrete trait are analogous. Variation of a quantitative trait x within the population is described by its probability density p(x), such that p(x)dx is the fraction of individuals within the population which possess the trait values between x and x +dx.

A distribution can be characterized by its moments. The most important of them are the first moment (mean) and the second central moment (variance):

$$M[p] = \int_{x_{min}}^{x_{max}} x p(x) dx \qquad (2.1.3.2\text{-}1)$$

$$V[p] = \int_{x_{min}}^{x_{max}} (x - M[p])^2 \, p(x) dx \qquad (2.1.3.2\text{-}2)$$

where x_{min} and x_{max} are the minimal and the maximal possible values of the trait, respectively. Often, instead of the variance, it is convenient to deal with the standard deviation of the trait, $\sigma = \sqrt{V[p]}$, which has the same dimensionality as the mean.

Indeed, the variance of body mass measured in grams is g^2, which may cause confusion. Higher-order moments, which describe asymmetry of the distribution and its other more subtle features, also may be useful.

A joint distribution of two quantitative traits x and y is described by the corresponding probability density r(x,y). The two traits are distributed independently if r(x,y) = p(x)q(y). Otherwise, non-independence of their distributions can be characterized by the coefficient of covariance

$$C_{x,y} = \int_{x_{min}}^{x_{max}} \int_{y_{min}}^{y_{max}} (x - M[p])(y - M[q]) r(x,y) dx dy \qquad (2.1.3.2\text{-}3)$$

Normalized measures of association (correlation) and asymmetric measures (regression) are also widely used. Quantitative traits with Gaussian, or normal distribution

$$p(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-(x-M)^2/(2\sigma^2)} \qquad (2.1.3.2\text{-}4)$$

are of particular importance. Such a trait is completely described by its mean M[p] and standard deviation σ[p] (Fig. 2.1.3.2a).

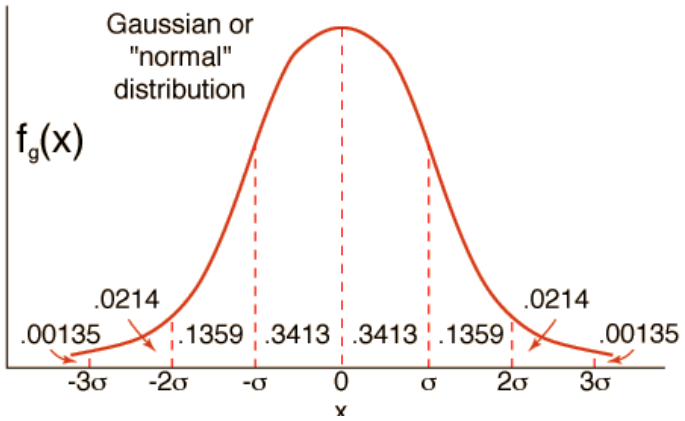

Fig. 2.1.3.2a. Properties of Gaussian distribution with M = 0.

In a variety of cases, we need to consider complex traits that can accept values that are not equally dissimilar from each other but also cannot be naturally ordered. There is no general theory of such traits, and each case is treated differently. Here it is sufficient to present three examples.

1. A segment of sequence consisting, for example, of 10 nucleotide sites. Clearly, some states of such a trait (*e. g.*, ATGCATGCAT and ATGCATGCAA) are closer to each other than others (*e. g.*, ATGCATGCAT and CGAAGCGTCC), but there is no natural order within this space of sequences.

2. Many phenotypic traits (*e. g.*, the shape of a wing) are, in effect, infinite-dimensional. Again, two shapes can be similar to different extents, but all possible shapes cannot be ordered in a useful way.

3. A trait may be an algorithm used by individuals in a particular situation. For example, individuals can form pairs and interact repeatedly within a pair. If you partner, before the current moment cooperated, defected, defected, and cooperated again (Chapter 3.4), what will you do? The answer depends on a particular algorithm you use for making this decision, and such algorithms can be rather complex.

2.1.3.3. Describing a variable population

The salient property of within-population genetic variation is that, if we ignore extremely rare variants, it can be naturally resolved into distinct variable traits (loci). This property follows from high levels of similarity between genotypes within a population. Typical values of H are 0.001 - 0.01 (Section 2.2.1) and alignments of different genotypes contain only rare gaps (Fig 2.1.3.3a). In fact, alignments of genomes of different species that are very similar to each other possess the same property (e. g., Fig. 1.4.1.3a). In contrast, alignments of multiple genomes of distant species (Chapter 1.5) may be impossible to resolve into distinct variable traits. Most of variable traits describing within-population variation are small-scale, and usually only two alleles have appreciable frequencies in each such trait (Fig 2.1.3.3a).

```
Genotype 1        CTCAAACaAATC---GGGCAAAAgGTGG-TATTGAcAGG
Genotype 2        CTCAAACaAATCggtGGGCAAAAtGTGG-TATTGAaAGG
Genotype 3        CTCAAACaAATCggtGGGCAAAAgGTGGaTATTGAcAGG
Genotype 4        CTCAAACgAATCggtGGGCAAAAgGTGG-TATTGAaAGG
```

```
Ancestral State   CTCAAACaAATCggtGGGCAAAAgGTGG-TATTGAaAGG

Genotype 1        GCTCCctAACGAAA    ...    GTAAAattgATCCC
Genotype 2        GCTCCgaAACGAAA    ...    GTAAA----ATCCC
Genotype 3        GCTCCgaAACGAAA    ...    GTAAAatcgATCCC
Genotype 4        GCTCCgaAACGAAA    ...    GTAAAattgATCCC
Ancestral State   GCTCCgaAACGAAA    ...    GTAAAattgATCCC
```

Fig. 2.1.3.3a. Typical structure of within-population variation of genotypes. (top) Variation can be resolved into distinct simple traits, mostly single-nucleotide substitutions, deletions, and insertions (relative to the ancestral genotypes). (bottom) Rarely, different traits can touch each other (left) or even overlap (right).

Every opportunity to simply things further, by lumping some elementary sequence-level traits together, should be used. For example, if we study the balance between deleterious mutations and negative selection against them within a protein-coding gene, all drastic sequence variants can be lumped into one allele, because different loss-of-function mutations of the gene have essentially the same impact on fitness (Fig. 2.1.3.3b).

```
HB407             17761,C→T   116,Arginine→Stop
Calgary 24        17756,-G    Frameshift
UK 246            17782,T→C   123,Serine→Proline
Sao Paulo 4       20360,T→G   Splicing acceptor splice
```

Fig. 2.1.3.3b. A sample of descriptions of loss-of function alleles of an X-linked gene that encodes the protein known as factor IX of blood coagulation in humans. Each allele has its own name, and is characterized by the nucleotide(s) affected, numbered according to their positions within the gene, by nature of the sequence change, and by its impact on the encoded protein or on splicing. None of these alleles encodes functional factor IX protein. Thus, when present in a male, each of these alleles causes severe hemophilia.

Complete description of genetic variation in some traits consists of frequencies of all the possible genotypes, *i. e.*, of combinations of alleles at all the polymorphic loci.

The number of such combinations, 2^n, for n diallelic loci, can be huge. However, a simpler description may be enough. In particular, frequencies of individual alleles at all the loci are sufficient to describe the population, as long as alleles of different loci are distributed approximately independently, which is often the case with amphimixis.

For example, let us consider a diploid population polymorphic at one locus A with two alleles A_1 and A_2. An individual in this population is fully characterized by the states of two structureless traits, corresponding to its maternal allele and its paternal allele, so that four genotypes A_1A_1, A_1A_2, A_2A_1, and A_2A_2 are possible. Then, a population fully described by frequencies of any 3 genotypes, because $[A_1A_1] + [A_1A_2] + [A_2A_1] + [A_2A_2] = 1$. However, we usually can treat the two reciprocal heterozygotes together, using the same notation (say, A_1A_2) for both of them. Then, there are only three genotypes A_1A_1, A_1A_2, and A_2A_2 , and the population can be described by frequencies of any two of them. To simplify things further, amphimixis with random mating leads to independent assortment of alleles and, if maternal and paternal allele frequencies are the same,

$$[A_1A_1] = [A_1][A_1] \qquad [A_1A_2] = 2[A_1][A_2] \qquad [A_2A_2] = [A_2][A_2] \qquad (2.1.3.3\text{-}1)$$

These relationships are known as Hardy-Weinberg law (Section 2.2.3). If so, only one number, for example the frequency of allele A_1, (because $[A_1] + [A_2] = 1$), is sufficient to describe the population.

Similarly, if we consider two diallelic loci A and B, two variables, frequencies of alleles $[A_1]$ and $[B_1]$, may sufficient to describe a haploid population, instead of any 3 of the 4 genotype frequencies ($[A_1B_1]$, $[A_1B_2]$, $[A_2B_1]$, and $[A_2B_2]$), as long as alleles at the two loci are distributed independently and $D_{A,B} = 0$ (2.1.3.1-3). When many variable loci are considered simultaneously and their alleles are not distributed independently, it may still be possible to take into account only pairwise associations between them, and ignore higher-order associations. In contrast, distributions of alleles at tightly linked loci may be so strongly correlated that only some combinations of their alleles, for example A_1B_1 and A_2B_2 are present at most moments. Such tightly linked loci may be approximately treated as one locus (Chapter 2.4).

Even knowing frequencies of all possible genotypes may be not enough. For example, with non-random mating and complex selection, we may need, in order to predict the dynamics of the population, to know frequencies of pairs of genotypes of individuals that breed with each other (Chaper 2.4). Fortunately, it seems that phenomena that require such descriptions are not central to Microevolution.

Description of within-population variation at the genome level requires by data on complete genotypes of many individuals. Such data are only rarely available and may be hard to interpret. Fortunately, deeply simplified descriptions, tailored to address a particular problem, are often feasible and sufficient. We should always strive to consider the smallest part of the genome that evolves more or less independently. The absolute fitness is determined by the whole genome, but relative fitnesses that depend on a part of the genome are sufficient, as a first approximation, to understand its evolution if natural selection affects it independently. This is guaranteed if the rest of the genome is monomorphic or is polymorphic but its variation is selectively neutral. Otherwise, contributions of the part of the genome under consideration and the rest of the genome into fitness must be independent, in the sense that fitness is the product of these contributions. In other words, the chief mechanism that entangles the dynamics of different parts of the genome is epistatic selection.

For example, suppose that two nucleotide sites (loci) encode a pair of nucleotides that interact with each other in the secondary structure of an RNA molecule. If this interaction is required to stabilize a stem structure, high fitness may be conferred by Watson-Crick pairs G:C (the best, due to 3 hydrogen bounds) and A:U (2 hydrogen bounds), as well as by a relatively stable G:U pair, while other pairs lead to lower fitness. Thus, selection acting on these two loci may look as shown in Fig. 2.1.3.3c. Clearly, neither of these loci can be studied separately: at each of them, A can be either inferior or superior to G, depending on which allele is currently common at the other locus.

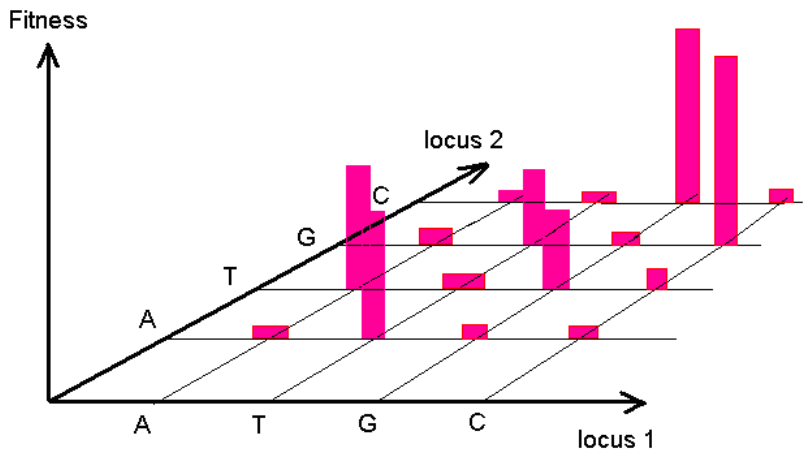

Figure 2.1.3.3c. Fitness landscape over two loci, corresponding to two sites that harbor nucleotides interacting in an RNA secondary structure.

If we are interested in the evolution of phenotypes, an attractive approach is to avoid any explicit consideration of genotype frequencies and, instead, to characterize the population only by its phenotypic variation. This approach, although generally insufficient, can produce some useful results (Chapter 2.4). However, subdividing phenotypes into traits is arbitrary to a much larger extent than in the case of genotypes.

Later in Part 2 we will encounter many theoretical analyses of Microevolution, using rather different descriptions of variable populations. We will see that success of such analyses depends on the suitable choice of this description. To understand Microevolution, we need to maintain the balance between tractability and completeness of the description of variation in an evolving population. Surprisingly, this can often be achieved.

2.1.3.4. Space of population compositions

An individual can be represented by a point within some space of genotypes (or phenotypes). Then, if we describe a variable population by frequencies of different (partial) genotypes, the population is represented by a small spot, a set of near-by points, within this space. Such a spot is small because genotypes that belong to the same population are similar to each other, and differences between then are mostly simple (Fig. 2.1.3.3a). Each point can be characterized by its "brightness", the frequency of the corresponding genotype. Microevolution of the population consists of movements of the

corresponding spot: new points appear, old points disappear, and some points get brighter or dimmer (Fig 2.1.3.4a).

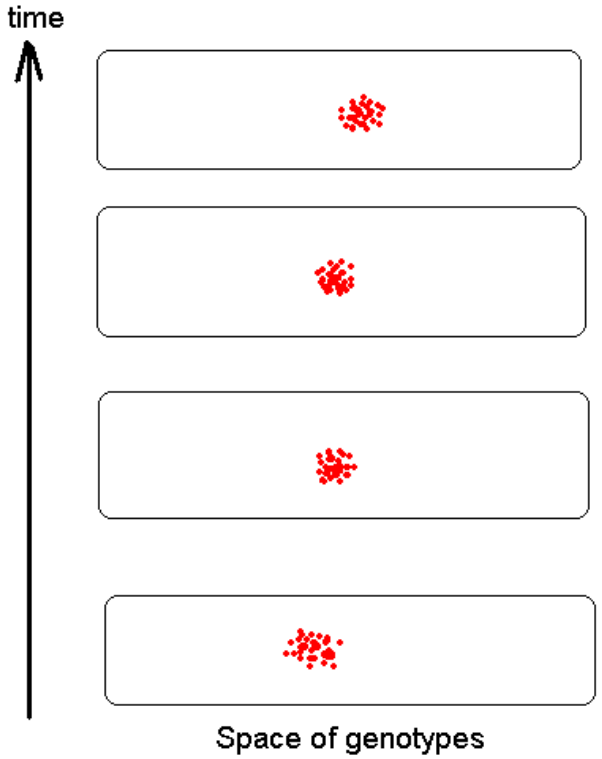

Fig. 2.1.3.4a. Microevolution as movement of a spot which represents a population in the space of genotypes.

Alternatively, we can device yet another space, the space of population compositions, such that each point of this space describes a variable population, *i. e.*, corresponds to a spot in the original space of genotypes. Then, Microevolution may be viewed as movements of the point which represents a population within this new space. Obviously, the exact nature of the space of compositions depends on how we describe the population. On the one hand, the space of compositions of a population can be "more complex" than its "parent" space of partial genotypes, because a spot in the later corresponds to just a point in the former. On the other hand, space of compositions can be simpler, if the description of the population does not include frequencies of all genotypes.

In the simplest case, if we consider haploids with one locus A and two alleles, A_1 and A_2, the space of (partial) genotypes that we take into account consists of just two

points. The corresponding space of compositions is the segment of a line from 0 to 1, as long as we describe the population by $[A_1]$ (which is sufficient, because $[A_1] + [A_2] = 1$) and assume that the population is large enough to treat $[A_1]$ as a continuous variable (Fig. 2.1.3.4b). The same space of compositions can be used to describe a diploid population, where 3 different genotypes can be present, as long as it obeys Hardy-Weinberg law.

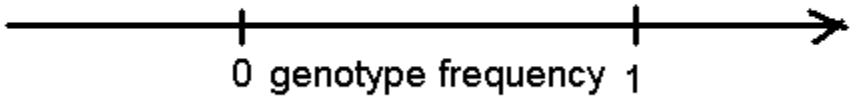

Fig. 2.1.3.4b. One-dimensional space of compositions of a population described by the frequency of one allele.

If we consider one haploid locus with 4 alleles, A, T, G, and C, the space of compositions of a population described by genotype frequencies is a part of a 3-dimensional cube (excluding one of the alleles, for example, C), limited by a plane [A] + [T] + [G] = 1 (Fig. 2.1.3.4c). Generally, the space of compositions has n-1 dimensions, when n different genotypes are possible.

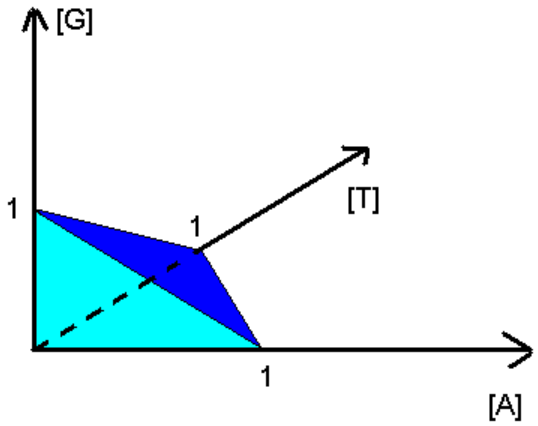

Fig. 2.1.3.4c. 3-dimensional space of compositions describing frequencies of 4 genotypes.

As an example of spaces of compositions that appear when the description of a population is radically simplified, let us consider a large number of diallelic loci at which beneficial mutations can occur. Then, a population is fully described by frequencies of all the possible 2^n genotypes. However, if we treat the number of beneficial alleles as fitness potential and describe the population by frequencies of individuals carrying all possible numbers x of beneficial alleles, the corresponding space of compositions consists of all possible distributions p(x). If we approximately assume that x is a continuous variable, the space of all possible distributions is, formally speaking, infinite-dimensional (Fig. 2.1.3.4d). Spaces of compositions that consist of distributions also appear if individuals within the population are described by a quantitative phenotypic trait, such as body mass.

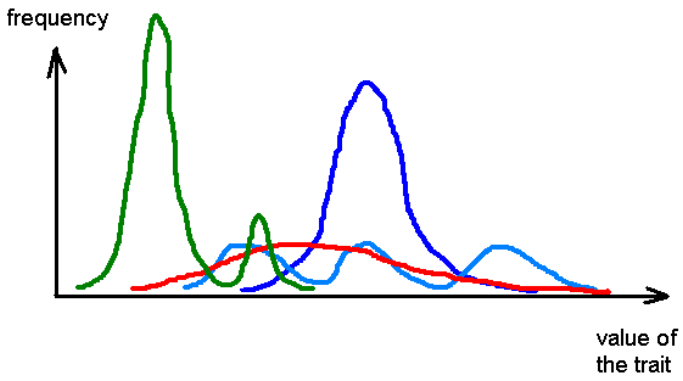

Figure 2.1.3.4d. Four points within the infinite-dimensional space of distributions of a continuous quantitative trait.

However, it is often possible to assume, as a good approximation, that the distribution of the trait can only be of some particular kind, such as Gaussian (2.1.3.2-4). The space of all Gaussian distributions is only 2-dimensional (Fig. 2.1.3.4e).

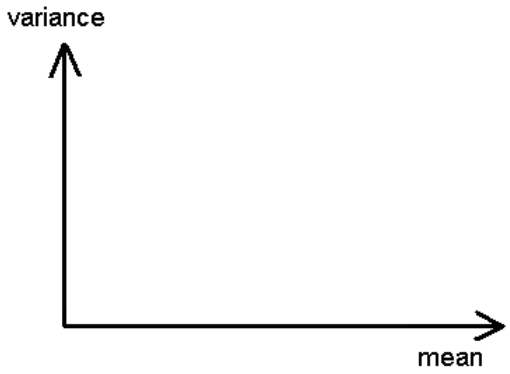

Figure 2.1.3.4e. Space of all possible Gaussian distributions.

Clearly, a space of compositions is just another, very useful, way of looking at a population, after its description has been chosen. We will use such spaces extensively.

2.1.3.5. Inferring properties of populations from samples

Studying a variable natural population consists of two steps. First, we need to ascertain the values of some trait(s) for some number of individuals that constitute a sample from the population. Indeed, to study every individual from a population is usually impossible. Second, we need to infer something about the population as a whole from the data on this sample. Here we will ignore the issue of obtaining data on individuals, which is really not a part of population biology and can use many methods, including DNA sequencing, simple measurements of body mass, or complex observations of behavior.

Instead, let briefly consider the second step, only in the simplest case when a property of the population that we want to know is a scalar parameter, such as the frequency of an allele or the mean body mass. How to deduce the hidden value of this unobservable parameter from the observed data, obtained from a sample? We already encountered the most commonly used approach to this problem, maximal likelihood (ML), when phylogenetic reconstructions were considered (Section 1.1.3.4). Here, our hypotheses H are different values of the unobservable parameter, and our data D are, in the simplest case, the value of this parameter observed within the sample. As before, we seek such a hypothesis that produces the data with the maximal probability, and interpret this probability P(D|H) as the likelihood of the hypothesis given the data. For example, if

500 individuals from a sample of size 1000 have genotype A_1 (D = 0.5), the ML estimate of H is also 0.5: the chances of finding exactly 50% of A_1 individuals within the sample are the highest when $[A_1] = 0.5$. In simple cases like this, the ML estimate of an unobservable parameter is unbiased: if we produce our estimate for many independent samples, the average of all these estimates would be equal to the real value of H.

A ML, or any other, estimate of H is just a number, which "most likely" corresponds to its real, unobservable, value. Because the chances of estimating H exactly are slim, we also need to know how good our estimate is. A natural way to address this issue is to introduce the concept of confidence interval with probability q. This is such an interval that included the true, unobservable value of H with probability q. 95% confidence intervals are commonly used (Fig. 2.1.3.5a).

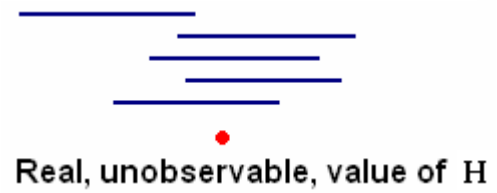

Fig. 2.1.3.5a. The concept of a confidence interval. 4 out of 5 independently computed intervals include the true value of the unobservable parameter H.

In a sample of K individuals, we will observe k A_1 individuals with the probability

$$p(H,k,K) = \binom{K}{k} H^k (1-H)^{K-k} \qquad (2.1.3.5\text{-}1)$$

In other words, under given H and K, k has a binomial distribution. The average value of our data D = k/K is H, and the standard deviation of D is $\sqrt{H(1-H)/K}$. It is easy to show that D is an unbiased ML estimate of H. When K is large enough, binomial distribution approaches Gaussian distribution. For a Gaussian distribution, the probability of deviating, in either direction, by more than 2 standard deviations from the mean is

~2.5% (Fig. 2.1.3.2a). Thus, 95% confidence interval for this estimate of H is k/H± $2\sqrt{(k/K)(1-k/K)/K}$.

Let us now consider estimating the mean value of a quantitative trait x. Every individual in a population is characterized by its own value of x, and the unobservable mean value of x is H. The unbiased ML estimate of H is simply the mean value of this trait within the sample of K individuals:

$$X = (1/K)\sum_{i=1}^{K} x_i$$

If we draw many samples, and determine X for each of them, this random variable will have a Gaussian distribution with a standard deviation $\sigma/\sqrt{K}$, where σ is the actual standard deviation of the trait within the population. Assuming that we know σ, the 95% confidence interval for our estimate of the mean value of the quantitative trait is

$$(1/K)\sum_{i=1}^{K} y_i \pm 2\sigma/\sqrt{K}$$

It is unrealistic to assume that we know the standard deviation when we do not know the mean. Thus, σ also has to be estimated from the same sample, but we will ignore this issue here. Obtaining estimates and the corresponding confidence intervals for other parameters of within-population variation, such as heterozygosity of an unstructured trait, variance of a quantitative trait, or association between two traits can also be done but also requires more complex calculations.

Not every property of a population is defined by genotypes or phenotypes of individuals at a particular moment of time. "Static" properties that can be defined in this way, such as allele frequencies, distributions of quantitative traits, or age structures, are, of course, very important. However, "dynamical" properties of populations, such as mutation rates, strengths of selection, or rates of migration are also crucial for Microevolution. Such dynamical properties and methods for estimating them are considered later in Part 2.

Section 2.1.4. Studying dynamics of within-population variation

Studies of any changes are based on investigating dynamical models. A dynamical model consists of a sufficiently detailed description of the changing object at a particular moment of time and of a transformation law that describes how these changes occur. The description of an object is provided by variables, and all possible combinations of their values constitute its phase space. Changes of the object can be represented by trajectories within the phase space. Simple dynamical models can be solved comprehensively, in the sense that all such trajectories can be explicitly found. For more complex models, only qualitative investigation, based on analysis of attractors, states in which the object can exist after a long time, is possible. The simplest attractors are equilibria. An attractor is stable if an object will return to it after a small deviation, and unstable otherwise. A dynamical model usually contains invariant parameters, and different regions of the space of these parameters may correspond to different modes of dynamics. Direct problem of dynamics consists of predicting changes of an object from known values of parameters that affect these changes. Inverse problem of dynamics consists of inferring unknown values of parameters from known changes of the object. It is convenient to build dynamical models of populations incrementally, starting from a trivial population in which nothing happens and taking factors of Microevolution into account one-by-one.

2.1.4.1. Structure of a dynamical model

To study how a natural object changes, we need to create its dynamical model, a mathematical object whose changes resemble that of the real object. A simple dynamical model consists of two components: 1) formal description of a state of the object at a particular moment of time and 2) transformation law, which connects the future of the object to its current state.

An evolving population, like any changing object, can be described by one or several numerical variables, functions, *etc*. (Section 2.1.3.4). Obviously, the simpler the description, the better. Still, the description must be dynamically sufficient, *i. e*. it must allow one to predict what will happen to the object in the future. For example, it is not

enough to specify just the total number of humans living in a village, in order to predict how many children will be born next year: at the very least, we must also know the age structure of the village population.

In addition to variables, a model usually contains parameters. Parameters do not change with time but, instead, can change "from case to case". For example, we may want to know how the frequency of an allele (variable) changes with time depending on the constant value of its selective advantage (parameter). Parameters make it possible to study a family of many similar models at once.

Time in a dynamical model may be continuous, at it is in nature, at least from the naive point of view of a biologist. However, if dynamics of an object are strongly affected by some external periodic process, time may also be treated as a discrete variable. For example, it is enough to describe a population with discrete, non-overlapping generations (*e. g.*, of an annual plant without dormant seeds) only once every year. Discrete-time and continuous-time models often have analogous dynamics, although discrete time can also lead to extra complications.

With discrete time, a transformation law f must specify, for every possible current state of the object x_n, the unique, as far as the model is deterministic, state of the object at the next moment of time: $x_{n+1} = f(x_n)$. With continuous time, where the notion of the next moment makes no sense, transformation law specifies the velocity at each current state: $dx/dt = f(x)$ (we will use n and t to refer to discrete and continuous time, respectively).

A deterministic transformation law can be visualized as vector field, an arrow growing from every point in the phase space. With discrete time, an arrow points to the state where the object will find itself in the next moment. With continuous time, an arrow indicates the velocity of the object, and trajectories describing its dynamics are tangential to these arrows.

Let us build and investigate a simple deterministic dynamical model with only one variable. Our goal is to illustrate the concepts just introduced and to develop the language which is required to understand any changes, including Microevolution. Thus, we do not need to approach this model with full mathematical rigor. More complex models will be introduced later, when necessary.

We will study the most important factor of Microevolution, natural selection, in the simplest situation. Consider a population of N individuals with just two possible

genotypes, A and a. We assume that individuals breed true, so that differences between these genotypes may involve any number of loci if reproduction is apomictic, but only one haploid locus with amphimixis (Section 2.3.3). Generations do not overlap, so that time in the model is discrete. The expected numbers of offspring of an individual of genotypes A and a are w_A and w_a, respectively. Unless w_A and w_a are identical, selection operates within the population. How will this constant selection affect genetic variation?

The numbers of offspring with genotypes A and a will be almost precisely $N[A]w_A$ and $N[a]w_a$, respectively, as long as N is large enough, so that stochasticity of reproduction of an individual can be ignored (we will omit subscript n when the current generation is considered). The frequency of A in the next generation, $[A]_{n+1}$, *i. e.* its frequency among the offspring, is provided by the ratio of the number of offspring of genotype A over the total number of offspring. Because [a] = 1 - [A], full description of our population consists of just one number, for example [A], and we obtain the following transformation law:

$$[A]_{n+1} = w_A[A]/\{w_A[A]+w_a(1-[A])\} \qquad (2.1.4.1\text{-}1)$$

It appears that dynamics of the population depends on two parameters, w_A and w_a. However, if we divide both the numerator and the denominator of the right-hand side of (2.1.4.1-1) by, say, w_A, we can see that this is not so:

$$[A]_{n+1} = [A]/\{[A]+(w_a/w_A)(1-[A])\} \qquad (2.1.4.1\text{-}2)$$

The following four statements summarize what we achieved so far:

1) if N is very large, the current state of the population exactly determines its next state, so that our model is deterministic,

2) the current state of the population is completely described by just one variable, the frequency of either genotype, so that the phase space of our model is one-dimensional,

3) the transformation law of our model does not depend of N, so that the size of the population can be ignored in this analysis of changes of its genetic variation,

4) only the ratio of fitnesses of the two genotypes, w_a/w_A, and not these fitnesses taken separately, determines the dynamics of the genotype frequencies. This is just another way of saying that in simple situations natural selection depends only on relative fitnesses.

Let us now create a continuous-time version of the same model. Dynamics with discrete and continuous time can be very different, because with discrete time an object can make long jumps between its successive states, undergoing large instant changes. Still, if we assume that natural selection is weak, *i. e*. that w_a and w_A are close to each other, there will be no long jumps and we can be sure that the changes of the genetic variation do not depend much on whether time is treated as discrete or continuous.

Let us define selective advantage of A over a as $s = 1 - w_a /w_A$. Obviously, $s = 0$ if fitnesses of A and a are equal, $s > 0$ if $w_a < w_A$, and $s < 0$ if $w_a > w_A$. Then, we can rewrite (2.1.4.1-2) as:

$$[A]_{n+1} = [A]/\{[A] + (1-s)(1-[A])\} = [A]/\{1 - s(1-[A])\} \qquad (2.1.4.1\text{-}3)$$

Selection is weak if s is small, so that w_a /w_A is close to 1. In this case, we can use an approximation $1/(1-\varepsilon) \approx 1 + \varepsilon + O(\varepsilon^2)$ (ε means a small number) to simplify (2.1.4.1-3):

$$[A]_{n+1} = [A] + s[A](1-[A]) \qquad (2.1.4.1\text{-}4)$$

Now let us treat time as continuous, and assume that velocity of [A], d[A]/dt, is equal to its increment between two successive moments in discrete-time treatment, $[A]_{n+1} - [A]$:

$$d[A]/dt = s[A](1-[A]) \qquad (2.1.4.1\text{-}5)$$

We arrived to a differential equation which represents the most important dynamical model in Microevolution, describing an allele replacement driven by natural selection.

Strikingly, essentially the same equation also plays the key role in population ecology, where it describes population growth with self limitation and is conventionally written as

$$dN/dt = rN(1-N/K) \qquad (2.1.4.1\text{-}6)$$

where r is the per capita growth rate and K is carrying capacity of the environment. This coincidence is particularly strange, because evolutionary biology and ecology approach populations from rather different perspectives. Studies of microevolution are mostly concerned with within-population variation, while population size can be often ignored. In contrast, population ecology concentrates on sizes and age- and spatial structures of populations, often ignoring their genetic variation.

Equation (2.1.4.1-5) is just a step more complex than the simplest possible differential equation dx/dt = rx describing unlimited, exponential growth or decline of a population (depending on the sign of r) or radioactive decay within a macroscopic sample (Section 1.2.2.1).

Graphical representations of the above models are also helpful. Fig. 2.1.4.1a shows two ways of presenting discrete-time dynamical model (2.1.4.1-2), and Fig. 2.1.4.1b does the same for continuous-time model (2.1.4.1-5).

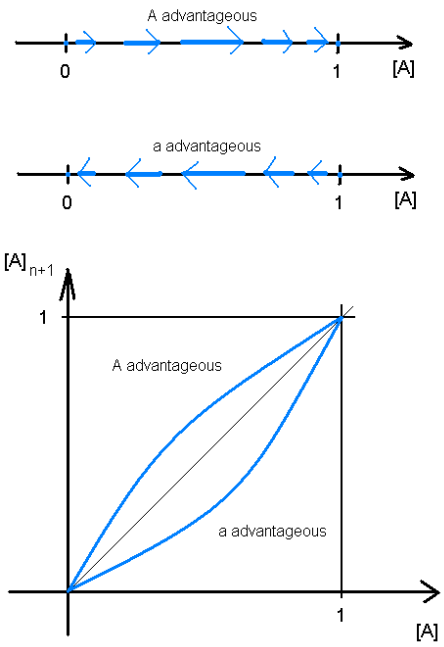

Fig. 2.1.4.1a. Two ways of presenting discrete-time dynamics (2.1.4.1-2) graphically: by vectors that describe jumps from a value [A] to the corresponding value of $[A]_{n+1}$ (two top figures; only seven, out of infinitely many, vectors are shown in each case) and by a function $[A]_{n+1} = f([A])$ (bottom). A is advantageous when $w_a/w_A < 1$; a is advantageous when $w_a/w_A > 1$; and selection is absent if $w_a/w_A = 1$ (what happens to the population in this case?).

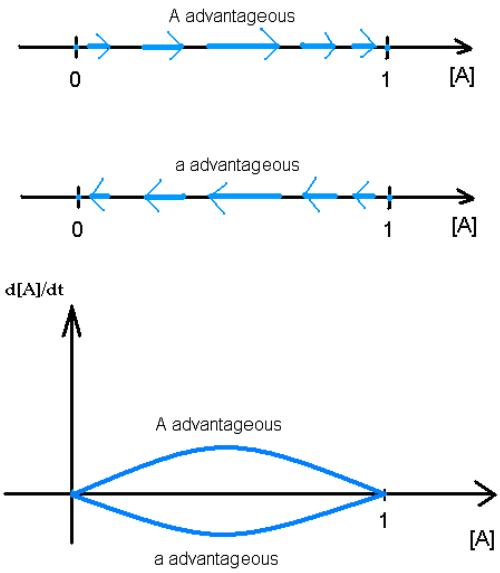

Fig. 2.1.4.1b. Two ways of presenting continuous-time dynamics (2.1.4.1-5) graphically: by vectors that describe velocities of [A] corresponding to its current values (two top figures; only seven, out of infinitely many, vectors, are shown for each case) and a by a function $d[A]/dt = f([A])$ (bottom). A is advantageous when $s > 1$; a is advantageous when $s < 1$; and if $s = 1$ selection is absent (what happens in this case?).

2.1.4.2. Comprehensive solution of a dynamical model

Let us now investigate the dynamics of an allele replacement in continuous time, described by (2.1.4.1-5). This differential equation can be solved comprehensively, in the sense that, under each value of s, changes of the frequency of A (and, thus, of a) can be found explicitly for every initial frequency of A, $[A]_0$. To make the following formulae more legible, let us now write x instead of [A]. We want to solve a differential equation:

$$\frac{dx}{dt} = sx(1-x) \qquad (2.1.4.2\text{-}1)$$

Using the mnemonics introduced in Section 1.2.2.1, we gather different variables at different sides

$$\frac{dx}{x(1-x)} = sdt \qquad (2.1.4.2\text{-}2)$$

and rewrite the differential equation in integral form:

$$\int_{x_0}^{x(t)} \frac{dy}{y(1-y)} = s\int_{t_0}^{t} d\tau \qquad (2.1.4.2\text{-}3)$$

The right-hand side integral is simply $s(t-t_0)$, and the left-side integral is

$$\int_{x_0}^{x(t)} \frac{dy}{y(1-y)} = \int_{x_0}^{x(t)} \frac{dy}{y} + \int_{x_0}^{x(t)} \frac{dy}{1-y} = \ln x(t) - \ln x_0 - \ln(1-x(t)) + \ln(1-x_0) \qquad (2.1.4.2\text{-}4)$$

because $\int \frac{1}{ay+b} dy = \frac{1}{a} \ln |ay+b|$. The right-hand side of (2.1.4.2-4) can also be written as $\ln \frac{x(t)}{1-x(t)} - \ln \frac{x_0}{1-x_0}$ or $\ln \frac{x(t)/(1-x(t))}{x_0/(1-x_0)}$. Thus,

$$\ln \frac{x(t)/(1-x(t))}{x_0/(1-x_0)} = s(t-t_0) \qquad (2.1.4.2\text{-}5)$$

We now need to recover x(t) from this equation. To simplify formulae, let us define $C_0 = \frac{x_0}{1-x_0}$. Then,

$$x(t)/(1-x(t)) = C_0 e^{s(t-t_0)} \qquad (2.1.4.2\text{-}6)$$

and

$$x(t) = C_0 e^{s(t-t_0)}/(1+C_0 e^{s(t-t_0)}) = 1/(1+(1/C_0)e^{-s(t-t_0)}) = 1/(1+\frac{(1-x_0)}{x_0}e^{-s(t-t_0)}) \qquad (2.1.4.2\text{-}7)$$

Formula (2.1.4.2-7) provides x(t) which is a solution of differential equation (2.1.4.2-1): if the velocity of allele A frequency is determined by (2.1.4.2-1), this frequency changes with time according to (2.1.4.2-7). In fact, (2.1.4.2-7) provides not just one x(t) but a one-parametric family of trajectories. Each trajectory corresponds to its own initial frequency of A, with the value x_0 at time t_0. Moreover, the dynamics of the frequency of A also depend on s, and for each value of s there exists its own family of trajectories. Naturally, x(t) increases with time if s > 0, decreases if s < 0, and does not change if s = 0 (Fig 2.1.4.2a).

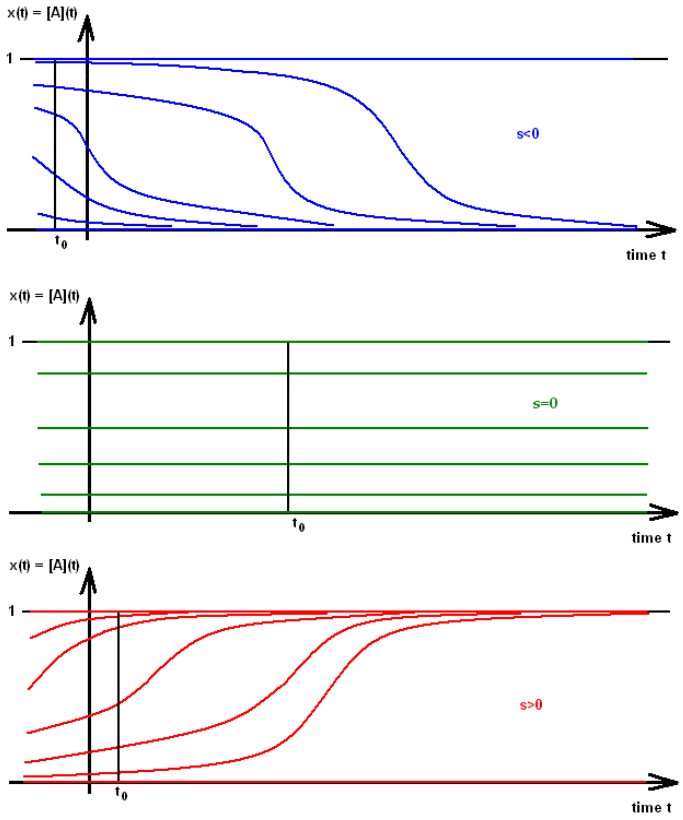

Fig 2.1.4.2a. Families of trajectories x(t), each having a particular value of the frequency of allele A at a moment t_0, that represent comprehensive solution of a dynamical model (2.1.4.2-1) that describes selection-driven allele replacement under three specific values of s, negative, zero, and positive.

All comprehensive solutions of dynamical models have the same structure, although they may, of course, depend on more than one parameter. However, only the simplest models can be solved like this. In particular, when a model contains of two or more variables, this is usually impossible. Moreover, even when a comprehensive solution exists, it may be too cumbersome to be useful. In both cases, a simplified approach can help.

2.1.4.3. Qualitative investigation of a dynamical model

In the model of an allele replacement we just considered (2.1.4.2-1), there are two exceptional initial frequencies of the allele A, $x_1 = 0$ and $x_2 = 1$. Trajectories with such initial frequencies are flat (2.1.4.2-7, Fig. 2.1.4.2a), *i. e*. if x is equal to 0 or to 1 at some moment, it never changes and retains this value forever. Biologically, this result is obvious: our model does not include mutation, so that if the population lacks either allele, this situation will persist.

Values of variables of a dynamical model that do not change with time are called equilibria. With $s > 0$, equilibrium $x_1 = 0$ is unstable, in the sense that a small deviation from it will increase and equilibrium $x_2 = 1$ is stable, because a small deviation from it will decrease. It is the other way around with $s < 0$. With $s = 0$, every value of x is an equilibrium, and all these equilibria are neutral, in a sense that deviations from them do not change (Fig 2.1.4.3a).

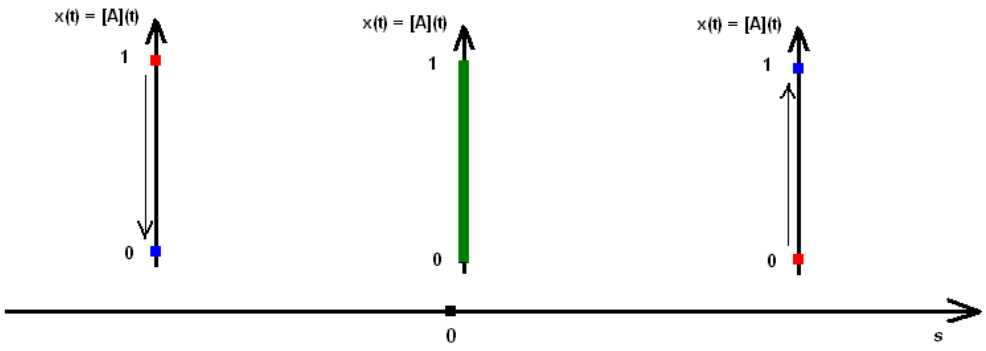

Fig 2.1.4.3a. Stable, unstable, and neutral equilibria are shown in blue, red, and green, respectively. With $s < 0$, fixation of allele a is stable and its loss is unstable. With $s > 0$, the same is true for fixation and loss of allele A. With $s = 0$, every allele frequency is a neutral equilibrium. Arrows show the direction of change of non-equilibrium allele frequencies.

Graphically, an equilibrium is a point within the phase space such that the vector growing from it is of zero length (Fig. 2.1.4.1a,b): with discrete time the state of the object in the next moment of time is identical to the current one, and with continuous time the velocity of the object is zero. One can also think of an equilibrium as a point where the graph of function that relates the next state of the object to its current state intersects the bisectrix of the positive quadrant (with discrete time), or the graph of function that relates the velocity of the object to its current state intersects the abscissa axis (with continuous time) (Fig. 2.1.4.1a,b).

This last interpretation of equilibria suggests the way of finding them algebraically. With discrete time, we need to substitute the next state in the left-hand side of the dynamic equation with its current state, thus stipulating that the next and the current states are identical. This procedure reduces a recurrence equation, such as (2.1.4.1-2), to an algebraic equation, which must then be solved. Applying this procedure to (2.1.4.1-2), we obtain

$$[A] = [A]/\{[A]+(w_a/w_A)(1-[A])\} \qquad (2.1.4.3\text{-}1)$$

which is a quadratic equation with two roots, $[A]_1 = 0$ and $[A]_2 = 1$. Only if $w_a/w_A = 1$, every value of [A] satisfies this equation.

With continuous time, to find equilibria we need to assume that the rate of change of the object is zero. This procedure reduces a differential equation, such as (2.1.4.1-5), to an algebraic equation:

$$0 = s[A](1-[A]) \qquad (2.1.4.3\text{-}2)$$

which has the same roots as (2.1.4.3-1).

Stability of an equilibrium is determined by whether small deviations from it increase or decrease. To investigate stability, let us expand the transformation law into Taylor series about the point of equilibrium and look at the linear term of this expansion. With discrete time, transformation law has a general form $x_{n+1} = f(x)$ and can be expanded, in the neighborhood of any point within the phase space x_0, as

$$f(x_0+\Delta x) = f(x_0) + df/dx|x_0\ \Delta x + ... \qquad (2.1.4.3\text{-}3)$$

where $\Delta x = x - x_0$ and $df/dx|x_0$ is a number equal to the derivative of f with respect to x, evaluated at point x_0. Now, if $x_0 = x_{eq}$ is an equilibrium, $f(x_{eq}) = x_{eq}$ (by definition of equilibrium), and the dynamics of a small deviation from it are approximately given by:

$$\Delta x_{n+1} = T\Delta x \qquad (2.1.4.3\text{-}4)$$

where $T = df/dx|x_{eq}$. There are 4 qualitatively different possibilities (Fig. 2.1.4.3b):

i) $T > 1$: instability, small deviation increase monotonously,

ii) $1 > T > 0$: stability, small deviation decline monotonously,

iii) $0 > T > -1$: stability, small deviation decline fluctuationally,

iv) $-1 > T$: instability, small deviation increase fluctuationally.

With continuous time, transformation law has the general form $dx/dt = f(x)$, its Taylor expansion in the neighborhood of a point x_0 is provided by (2.1.4.3-3), and, because in this case $f(x_{eq}) = 0$ and $d\Delta x/dt = dx/dt$, the dynamics of a small deviation from an equilibrium are described by

$$d\Delta x/dt = T\Delta x \qquad (2.1.4.3\text{-}5)$$

Thus, Δx increases monotonously if $T > 0$ (instability) and decreases monotonously if $T < 0$ (stability), and fluctuations are impossible in this case. These results can be easily understood graphically (Fig. 2.1.4.3b).

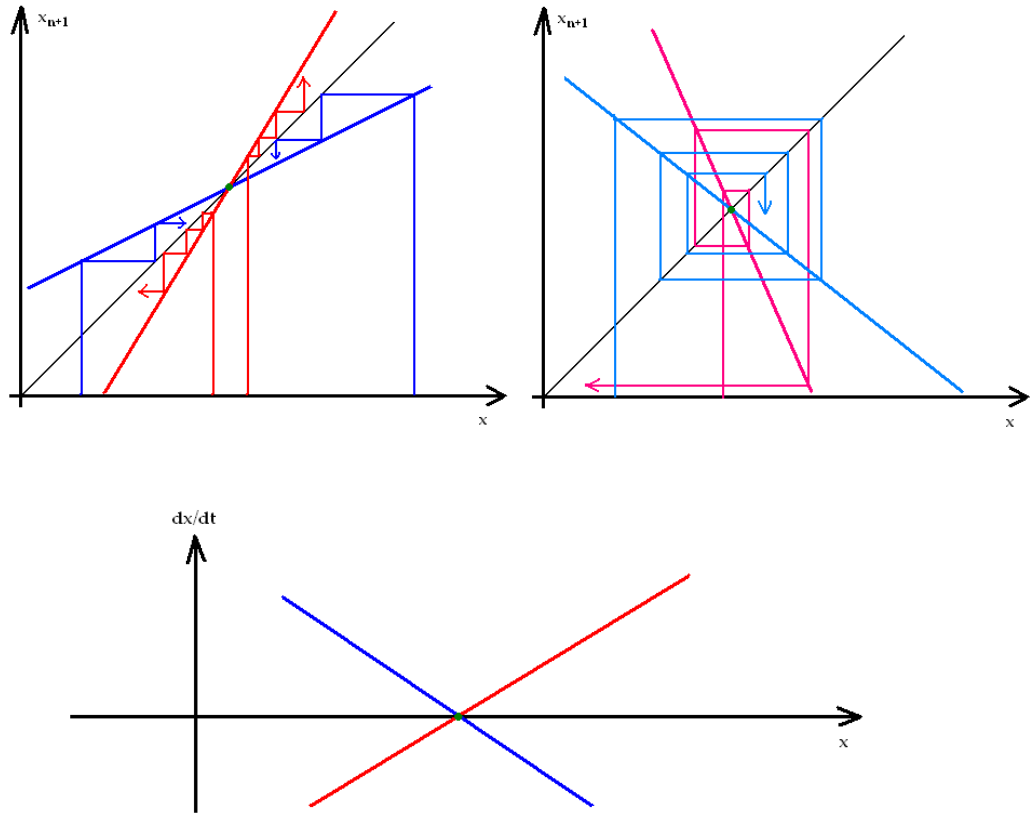

Fig. 2.1.4.3b. Graphical analysis of stability of an equilibrium with discrete (top) and continuous (bottom) time. Horizontal segments of ladders that describe dynamics with discrete time represent increments of time.

Let us apply this analysis to our model of selection. From (2.1.4.1-2), it is easy to see that $T = w_A/w_a$ at $x_1 = 0$ and $T = w_a/w_A$ at $x_2 = 1$, so that with discrete time and arbitrary selection fixation of an allele is unstable when it is disadvantageous and stable otherwise. From (2.1.4.1-5), $T = s$ at x_1 and $T = -s$ at x_2, implying that qualitative properties of the model remains the same with continuous time.

To complete qualitative investigation of the model, we need to understand transitions between its qualitatively different modes of dynamics that correspond to different regions in the one-dimensional space of parameters. Here, there are three such regions: $s < 0$, $s = 0$, and $s > 0$ (Fig. 2.1.4.3a). When, for example, a negative s starts increasing slowly (so it not, strictly speaking, an invariant parameter any more), the rate of decline of trajectories describing changes of allele A frequencies will diminish, until

everything freezes at s = 0, after which the frequencies will start growing slowly (Fig. 2.1.4.3c).

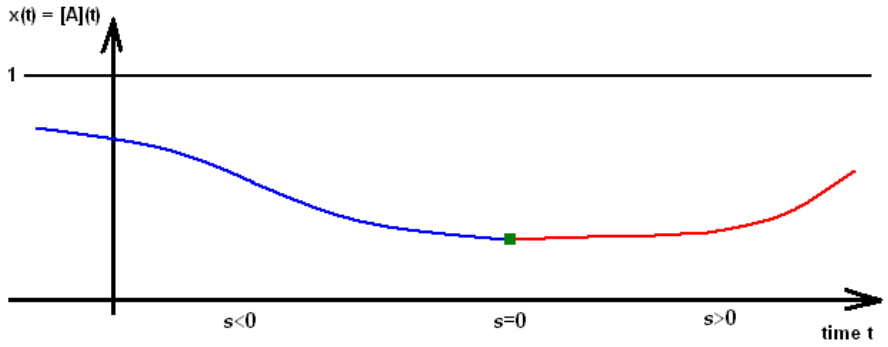

Fig. 2.1.4.3c. One trajectory describing changes in allele A frequency when s, initially negative, increases slowly.

Often, much more complex models must be studied. In particular, we may need to consider simultaneously the dynamics of two or more interacting variables, for example, if epistatic selection acts on two or more polymorphic loci. In multivariable models, more complex attractors, such as limit cycles and "strange attractors" are possible; in fact, they may appear even in single-variable models with discrete time. Such complex attractors are very important in ecological models, but, apparently, the dynamics of genetic variation is usually not that complex. Analysis of stability of equilibria and other attractors in multivariable models can also become rather technically involved, although the main idea, to determine whether small deviations from an attractor will increase (instability) or decrease (stability) remains the same. Finally, a model can have many parameters, and transitions between qualitatively different modes of its dynamics, called bifurcations, can be much more complex than what we just encountered. We will encounter several kinds of bifurcations in Chapters 2.3 and 2.4.

2.1.4.4. Direct and inverse problems of dynamics

So far, we approached studies of dynamics from what could be called a direct perspective: on the basis of knowledge of the transformation law and its parameters, we tried to predict how the population will change in the future, or, perhaps, to reconstruct its changes in the past. However, quite often values of parameters are not known *a priori*.

In particular, when we observe two alleles segregating within the population, it is may be impossible to determine their fitnesses by a simple measurement. Thus, the inverse perspective on dynamics, consisting of inferring the unknown values of parameters from data on population variation, is also very important. There is an obvious parallel between inferences of parameters that affect the dynamics of within-population variation from data on this variation, provided by application of dynamical models, and inferences of parameters of the whole population from data on samples, treated by statistics.

The case of simple selection-driven allele replacement considered above can be used to illustrate this perspective. Obviously, knowing only the current frequency of allele A is not enough to infer its relative fitness. However, if we also know how the frequency changes, s, in theory, can be easily inferred. Indeed, s can be recovered from (2.1.4.2-1):

$$s = \frac{dx/dt}{x(1-x)} \qquad (2.1.4.4\text{-}1)$$

Thus, if the frequency of allele A changed from 50% to 51% in one generation, its selective advantage must be 0.04. Trouble is, selection coefficients are usually much smaller than that and it is impossible to reliably measure small changes in allele frequencies caused by action of weak selection in the course of just one or several generations. In fact, we may need not only to measure the selection coefficient describing selection at a particular locus, but to ascertain epistasis, the shape of the fitness landscape, and the general mode of selection. Moreover, dynamics of allele frequencies can be affected by many other forces, in addition to selection, so that not only the value of the parameters, but the very transformation law needs to be inferred. Thus, inverse problems are among the most difficult in studies of Microevolution (Section 2.4.5).

2.1.4.5. Building dynamical models of Microevolution

Evolving populations are so complex that creating their models that are neither oversimplified nor intractable is a tough challenge. Several considerations can help to accomplish this task. In particular, it is useful to be aware of two contrasts between

dynamics of non-living and living objects. First, physics often studies models of non-living objects that are simple enough to be useful but still are rather close to reality. This is the case because a physical object can be simple. For example, a material point affected by Newtonian gravity provides a very useful model of the orbital movement of the Earth, and if this model is too crude, a more realistic version, treating the Earth and the Sun as spheres, is still tractable (Section 1.2.1.1). In contrast, biology deals with very complex objects and thus has to consider models that are profoundly simplified, because more realistic models would be useless.

Second, fundamental laws of physics are "fragile". If gravity were inversely proportional not to the square of the distance between objects, but to the distance up to the power of 2.00001, there would be no closed orbits of planets. If conservation of energy, charge, or some other physical quantity were not exact, the Universe would be drastically different. Mathematically, models that describe such fragile dynamics are "pathological", since their properties are exceptional, and even a small change of the model would radically alter its properties. In contrast, dynamical models used in biology are mathematically healthy and robust: a small alteration affects them only slightly.

An important issue is whether to consider deterministic or stochastic models. The law of large numbers often makes dynamics of populations approximately deterministic, despite stochasticity of individual events that occur within populations. The idea that the collective outcome of many individually stochastic events may often be treated as deterministic permeates all natural sciences (Section 1.2.2.1). Elementary populational events that, like decays of individual atoms, are stochastic include occurrences of individual mutations and cross-overs, acts of survival, mating, and reproduction of individuals, their movements in space, *etc*.

Naturally, stochastic models are much more complex than deterministic. Thus, we will treat dynamics of large populations as deterministic, for as long as this is tenable (Fig. 2.1.4.5a). This approach is surprisingly productive for analysis of mutation and selection, although stochasticity is still crucial for many key aspects of Microevolution (Chapters 2.2-2.5).

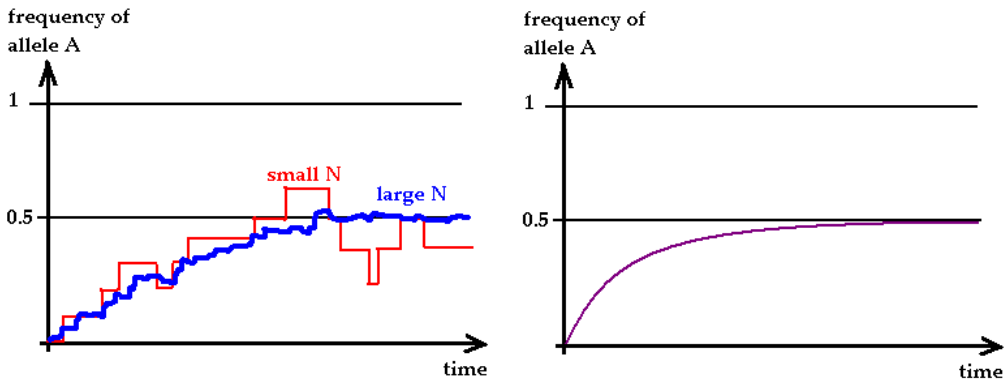

Fig. 2.1.4.5a. Exact stochastic (left) and approximate deterministic (right) treatment of the dynamics of a population where two alleles, A and a, can mutate into each other at equal rates, assuming that initially only allele a is present. Individual mutational events occur at random moments and shift frequencies of the alleles by 1/N, where N is the population size. Dynamics of allele frequencies are approximately deterministic, and allele frequencies eventually become very close to the deterministic equilibrium 1/2, if N is large enough (Section 2.3.1.2).

It is convenient to build dynamical models of Microevolution incrementally. We can start from a dumb population in which nothing happens. Such a population consists of some number of individuals that are all of the same age, live in the same place, and reproduce apomictically with each of them always leaving one offspring which is genetically identical to the mother. Although in this unrealistic case each lineage can be considered separately (Fig. 2.1.1.1b), let us treat all of them as a population. Naturally, each state of variation (*i. e.*, a set of allele frequencies, or a distribution of a quantitative trait) within such a population is a neutral equilibrium, because this population would never change.

Then, we can think of a questionnaire, consisting of 5 broad questions, which needs to be filled in order to specify a useful model of a real population. These questions correspond to the 5 factors of Microevolution, described in Chapter 2.3. The original dumb population has no mutation, no selection, is apomictic, has no structure, and does not experience drift, and now we need to introduce at least some of these factors. Depending on the number of "non-trivial" answers, we can get one- or many-factor

models. Above, we considered a one-factor model which involved only selection acting in the simplest possible way.

In Chapter 2.3, we will deal with all the 5 kinds of one-factor models. Such models are essential to understand the role of the corresponding factors of Microevolution and provide the necessary background for studying realistic, polyfactorial models. Chapter 2.4 will consider such models, and in Chapters 2.5 and 2.6 they will be applied to reality. Surprisingly, the right balance between tractability and complexity of a model can often be struck.

History and perspectives

Populations were introduced in biology as a part of Darwinian revolution, because natural selection is a population-level phenomenon. R. A. Fisher, in his classical book "The Genetical Theory of Natural Selection" (1930), was apparently the first one to argue that both ecological equivalence and outcrossing, when present, create populations out of individuals. In the XX century, population ecology and population genetics mostly developed independently of each other.

Fitness landscapes were introduced, in a form slightly different from that used currently, by Sewall Wrigth in his classical paper "Evolution in Mendelian Populations" (1931). Since then, thinking in terms of fitness landscapes slowly permeated all evolutionary biology. In particular, fitness landscapes over sequence spaces were first considered by John Maynard Smith in 1970. Surprisingly, fitness landscapes did not yet become a foundation for teaching evolutionary biology, and I am trying to rectify this. A number of papers can be mentioned in connection with the concept of fitness potential, the most important of them being the papers by J. L. King, R. D. Milkman, and J. A. Sved, T. K. Reed and W. F. Bodmer, published in the same issue of Genetics in 1967. The importance of negative and stabilizing selection has been emphasized by Ivan I. Schmalhausen, and epistasis has been considered very early by S. Wright, Hermann J. Muller, and Theodosius G. Dobzhansky, among others.

The science of statistics was developed to a large extent due to demand from studies of populations. Francis Galton, Karl Pearson, and R. A. Fisher, among the others, played a crucial role in this. The first systematic analysis of within-population genetic

variation at the DNA level was published in 1983 by Martin Kreitman. Non-independent distributions of alleles at different loci were first systematically treated by Motoo Kimura in 1956 and by Richard C. Lewontin and Ken-ichi Kojima in 1960. Hardy-Weinberg law, which make it possible to simplify the dynamically sufficient description of a diploid population, has been proposed independently by a mathematician Godfrey Hardy and a physician Wilhelm Weinberg in 1908.

Dynamical models were invented by Newton. Today, theory of dynamical models is the cornerstone of mathematical investigation of all natural phenomena. Mathematical studies of Microevolution were pioneered in early XX century by Fisher, Wright, and J. B. S. Haldane.

Perspectives. The populational foundations of Microevolution, and the framework for its studies provided by consideration of fitness landscapes and by statistical and dynamical analysis of genetic variation are not going to change. However, fitness landscapes of natural populations remain poorly known, and studying them is the key task of research in Microevolution. It seems that dynamics of genetic variation are usually not too complex. In contrast, inverse problems of dynamics, applied to models of natural populations, are often very complex and will remain an active area of research at the interface between biology, theory of dynamical systems, and statistics.