Migration-Selection Models in Population Genetics

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Contents

1 Introduction

Population genetics is concerned with the study of the genetic composition of populations. This composition may be changed by selection, mutation, recombination, mating behavior and reproduction, migration, and other genetic, ecological, and evolutionary factors. Therefore, in population genetics these mechanisms and their interactions and evolutionary consequences are investigated. Traditionally, population genetics has been applied to animal and plant breeding, to human genetics, and more recently to ecology and conservation biology. It also has important interfaces with molecular biology, systematics, natural history, mathematics, statistics, and computing. One of the main subjects is the investigation of the mechanisms that generate and maintain genetic variability in populations, and the study of how this genetic variation, shaped by environmental influences, leads to evolutionary change, adaptation, and speciation. Therefore, research in population genetics relies on empirical observations, on experiments, on data analysis, and on the study of mathematical models. In particular, population genetics provides the basis for understanding the evolutionary processes that have led to the diversity of life we encounter and admire.

Mathematical models and methods have a long history in population genetics, tracing back to Gregor Mendel, who used elementary mathematics to calculate the expected frequencies of the genes in his experiments. Francis Galton and the biometricians, notably Karl Pearson, developed new statistical methods to describe the distribution of trait values in populations and to predict their change between generations. The foundations of modern population genetics were laid by the work of Ronald A. Fisher, J.B.S. Haldane, and Sewall Wright, who reconciled Mendelism with Darwinism during the second and third decades of the twentieth century. They demonstrated that the theory of evolution by natural selection, proposed by Charles Darwin (1859), can be justified on the basis of genetics as governed by Mendel's laws. The work of Fisher, Haldane, and Wright was highly mathematical for the biology of that time and was properly understood by only a small number of people. Nevertheless, their influence was enormous and they set the standards for mathematical modeling and for rigor of theoretical investigations for the subsequent decades.

Prior to 1900, the year when Mendel's work was rediscovered and then rapidly accepted, the hereditary mechanisms were unknown. Darwin believed in blending inheritance, according to which the hereditary material itself blended. However, as already noted by Darwin, blending inheritance produces uniformity and destroys variation that is

so ubiquitous. In modern terms, heritable variance would be halved in each generation of random mating with blending inheritance (Fisher 1930). Therefore, one half of the heritable variance maintained in a population would have to arise anew in each generation. There were controversial lines of thought about the nature of this huge amount of new variation and its consequences for evolution. The `gradualists', to which Darwin and the biometricians adhered, considered the changes across generations as gradual and incremental, whereas the `saltationists' (e.g., T.H. Huxley and Galton) held that evolutionary changes occurred in `jumps' of considerable magnitude. Much of the scienti c dispute about Darwin's theory of evolution originated from the ignorance of the true hereditary mechanisms.

Despite the early work of Yule (1902), Hardy (1908), and Weinberg (1908), who showed that under the particulate mode of inheritance proposed by Mendel (1866), genetic variability is preserved under random mating, it was not before 1918 that the synthesis between genetics and the theory of evolution through natural selection began to take shape through Fisher's (1918) work (see Provine (1971) for a detailed account of the history of population genetics).

Today, the hereditary mechanisms have been rmly established and our knowledge about the molecular biology of the genes is rapidly increasing. Mutations are known to be the ultimate source of genetic variability, and many di erent processes at the chromosomal and molecular level have been identi ed that generate mutations. On the phenotypic level, the role of selection in shaping evolutionary change has been amply documented, whereas on the molecular level, a signi cant amount of neutral evolution appears to take place, its extent still being disputed. Nevertheless, there remain many open problems, some of which are qualitative in nature and some quantitative. Questions concerning the processes involved in speciation or in the evolution of sex belong to the rst class, whereas questions concerning the prediction of the expected evolutionary change of a population subject to selection belong to the second class. Such predictions are highly nontrivial, unless con ned to one or a few generations, because there exist many di erent forms of selection and the response to selection depends on the pattern and amount of genetic variability in the population. This variation, however, is a function of many genetic details (such as number of genes determining a trait, mutational properties, degree of linkage), of the demography (population size, mating structure), and of the selective forces acting. Therefore, the genetic variability may change from one generation to the next.

Mendel's (1866) prime achievement was the recognition of the particulate nature of the hereditary determinants, now called genes. A gene may have di erent forms, called $alleles$.

From his experiments with peas he concluded that genes are present in pairs, one member of each pair having been inherited from the maternal parent, the other from the paternal. Such organisms are called diploid. The allelic composition is called the $genotype$, and the set of observable properties derived from the genotype is the $phenotype$. Thus, supposing that there are two alleles $\mathcal{A}_1$ and $\mathcal{A}_2$, there are three possible genotypes, $\mathcal{A}_1\mathcal{A}_1$, $\mathcal{A}_1\mathcal{A}_2$, and $\mathcal{A}_2\mathcal{A}_2$. In the first and third case, the organism's genotype is $homozygous$ (for $\mathcal{A}_1$ or $\mathcal{A}_2$, respectively), in the second case it is $heterozygous$. In general, the genotypes $\mathcal{A}_1\mathcal{A}_2$ and $\mathcal{A}_2\mathcal{A}_1$ cannot be distinguished. When the phenotype of the heterozygote $\mathcal{A}_1\mathcal{A}_2$ is the same as one of the homozygotes, say $\mathcal{A}_1\mathcal{A}_1$, allele $\mathcal{A}_1$ is called $dominant$ and $\mathcal{A}_2$ is called $recessive$.

Meiosis is the process of formation of reproductive cells, or $gametes$ (in animals, sperm and eggs), from somatic cells. Under so-called $Mendelian\ segregation$, each gamete contains precisely one of the two alleles of the diploid somatic cell and each gamete is equally likely to contain either one. The separation of the paired alleles from one another and their distribution to the gametes is called $segregation$ and occurs during $meiosis$. At mating, two reproductive cells fuse and form a $zygote$ (fertilized egg), which contains the full (diploid) genetic information.

Since the 1940s it has been known that the genetic material is $deoxyribonucleic\ acid$ (DNA). It consists of four bases: adenine (A), guanine (G), thymine (T), and cytosine (C). Each base is linked to a sugar and a phosphate group, yielding a $nucleotide$. The nucleotides are arranged along two chains to form a double-stranded helix in which the pairings A{T and G{C between the strands are formed. Therefore, all the genetic information is contained in each of the two strands. Three bases code for one amino acid, which are the building blocks of polypeptide chains and proteins. A gene typically represents a contiguous region of DNA coding for one polypeptide chain. Its position along the DNA is called the $locus$, and a particular sequence there is called an allele. Thus, two genes at the same locus, sampled from a population, may or may not be of the same allelic type. A double-stranded helix of DNA forms the backbones of the $chromosomes$, which are contained in the nucleus of each cell. In $diploid$ organisms (higher plants and animals) chromosomes form homologous pairs, each one inherited from one parent. The exceptions are the $sex\ chromosomes$, which are involved in the genetic determination of sex. Usually, this is one pair of chromosomes which di er from each other, one called the X-chromosome, the other the Y-chromosome. In all mammals, in $Drosophila$, and in many other species and taxa, but not in birds, XX is female and XY is male. The term $autosome$ is used for chromosomes that are not sex chromosomes. The number of di erent

chromosomes per nucleus is characteristic of each species.

Any heritable change in the genetic material is called a *mutation*. Mutations are the ultimate source of genetic variability and form the raw material upon which selection acts. Although the term mutation includes changes in chromosome structure and number, the vast majority of genetic variation is caused by changes in the DNA sequence. Such mutations occur in many different ways, for instance as base substitutions, in which one nucleotide is replaced by another, as insertions or deletions of DNA, as inversions of sequences of nucleotides, or as transpositions. For many population-genetic models the molecular origin of a mutant is of little relevance. What often only counts is the rate at which mutations occur and the mutants' effect on fitness or, more generally, on the trait under consideration. Typically, spontaneous mutation rates per locus per generation are of the order of 10^{-4} to 10^{-6}, and genomic mutation rates summed over all loci may be on the order of one per generation, but can vary substantially between species.

During meiosis, different chromosomes assort independently and *crossing over* between two homologous chromosomes may occur. Consequently, the newly formed gamete contains maternal alleles at one set of loci and paternal alleles at the complementary set. This process is called *recombination*. Since it leads to random association between alleles at different loci, recombination has the potential to combine favorable alleles of different ancestry in one gamete and to break up combinations of deleterious alleles. These properties are generally considered to confer a substantial evolutionary advantage to sexual species relative to asexuals.

The mating pattern may have a substantial influence on the evolution of gene frequencies. The simplest and most important mode is *random mating*. This means that matings take place without regard to ancestry or the genotype under consideration. It seems to occur frequently in nature. For example, among humans, matings within a population appear to be random with respect to blood groups and allozyme phenotypes, but are nonrandom with respect to height.

Selection occurs when individuals of different genotype leave different numbers of progeny because they differ in their probability to survive to reproductive age (*viability*), in their mating success, or in their average number of produced offspring (*fertility*). Darwin (1859) recognized and documented the central importance of selection as the driving force for adaptation and evolution. Since selection affects the entire genome, its consequences for the genetic composition of a population may be complex. Selection is measured in terms of *fitness* of individuals, i.e., by the number of progeny contributed to the next generation. There are different measures of fitness, and it consists of several

components because selection may act on each stage of the life cycle.

For mathematically oriented introductions to population genetics, we refer to the books of Nagylaki (1992), Bürger (2000), from which much of this introduction is taken, Ewens (2004), and Wakeley (2008). The two latter texts treat stochastic models in detail, a topic ignored in this survey.

These lecture notes are devoted to a treatment of some of the most important aspects of the theory of migration-selection models. Because many natural populations are geographically structured and selection varies spatially due to heterogeneity in the environment, it is important to study the consequences of spatial structure for the evolution of populations. Dispersal of individuals is usually modeled in one of two alternative ways, either by diffusion in space or by migration between discrete colonies, or demes. If the population size is sufficiently large, so that random genetic drift can be ignored, then the first kind of model leads to partial differential equations (Fisher 1937, Kolmogorov et al. 1937). This is a natural choice if genotype frequencies change gradually along an environmental gradient, as it occurs in a cline (Haldane 1948). Here we will not be concerned with this wide and fruitful area and instead refer to Barton (1999), Nagylaki and Lou (2008), Lou et al. (2013) for recent developments and references.

Instead, we will investigate models of selection and migration between discrete demes. They originated from the work of Haldane (1930) and Wright (1931). Most of the existing theory has been devoted to study selection on a single locus in populations with discrete, nonoverlapping generations that mate randomly within demes. However, advances in the theory of multilocus models have been made recently. The general goal is to study the influence of population subdivision and of gene flow among subpopulations on the amount and pattern of genetic variation maintained. The models are typically formulated in terms of systems of nonlinear difference or differential equations. Thus, their analysis plays a central role and leads to interesting mathematical results.

Material that can be skipped on a first reading is set in smaller font and indented.

2 Selection on a multiallelic locus

Darwinian evolution is based on selection and inheritance. In this section, we summarize the essential properties of simple selection models. Proofs and a detailed treatment may be found in Chapter I of Bürger (2000). Our focus is on the evolution of the genetic composition of the population, but not on its size. Therefore, we always deal with relative frequencies of genes or genotypes within a given population.

Unless stated otherwise, we consider a population with discrete, nonoverlapping generations, such as annual plants or insects. We assume two sexes that need not be distinguished because gene or genotype frequencies are the same in both sexes (as is always the case in monoecious species). Individuals mate at random with respect to the locus under consideration, i.e., in proportion to their frequency. We also suppose that the population is large enough that gene and genotype frequencies can be treated as deterministic, and relative frequency can be identified with probability. Then the evolution of gene or genotype frequencies can be described by difference or recurrence equations. These assumptions reflect an idealized situation which will model evolution at many loci in many populations or species, but which is by no means universal.

We begin with the law of Hardy and Weinberg which formulates an extremely important consequence of Mendelian inheritance.

2.1 The Hardy–Weinberg Law

With the blending theory of inheritance variation in a population declines rapidly, and this was one of the arguments against Darwin's theory of evolution. With Mendelian inheritance there is no such dilution of variation, as was shown independently by the famous British mathematician Hardy (1908) and, in much greater generality, by the German physician Weinberg (1908, 1909).

We consider a single locus with I possible alleles $\mathcal{A}_i$ and write $\mathsf{I} = \{1, \ldots, I\}$ for the set of all alleles. We denote the frequency of the ordered genotype $\mathcal{A}_i\mathcal{A}_j$ by P_{ij}, so that the frequency of the unordered genotype $\mathcal{A}_i\mathcal{A}_j$ is $P_{ij} + P_{ji} = 2P_{ij}$. Subscripts i and j always refer to alleles. Then the frequency of allele $\mathcal{A}_i$ in the population is

$$p_i = \sum_{j=1}^{I} P_{ij} \,.^{1}$$

After one generation of random mating the zygotic proportions satisfy[2]

$$P'_{ij} = p_i p_j \qquad \text{for every } i \text{ and } j \,.$$

A mathematically trivial, but biologically important, consequence is that (in the absence of other forces) gene frequencies remain constant across generations, i.e.,

$$p'_i = p_i \quad \text{for every } i \,. \tag{2.1}$$

[1] If no summation range is indicated, it is assumed to be over all admissible values; e.g., $\sum_i = \sum_{i \in \mathsf{I}}$

[2] Unless stated otherwise, a prime, $'$, always signifies the next generation. Thus, instead of $P_{ij}(t)$ and $P_{ij}(t+1)$, we write P_{ij} and P'_{ij} (and analogously for other quantities).

In other words, in a (su ciently large) randomly mating population reproduction does not change allele frequencies. A population is said to be in $Hardy–Weinberg\ equilibrium$ if

$$P_{ij} = p_i p_j \,. \tag{2.2}$$

In a (su ciently large) randomly mating population, this relation is always satis ed among zygotes.

Evolutionary mechanisms such as selection, migration, mutation, or random genetic drift distort Hardy-Weinberg proportions, but reproduction restores them if mating is random.

2.2 Evolutionary dynamics under selection

Selection occurs when genotypes in a population di er in their tnesses, i.e., in their viability, mating success, or fertility and, therefore, leave di erent numbers of progeny. The basic mathematical models of selection were developed and investigated in the 1920s and early 1930s by Fisher (1930), Wright (1931), and Haldane (1932).

We shall be concerned with the evolutionary consequences of selection caused by differential viabilities (i.e., the probability that an o spring survives to reproductive age). Suppose that at an autosomal locus the alleles $\mathcal{A}_1, \ldots, \mathcal{A}_I$ occur. We count individuals at the zygote stage and denote the (relative) frequency of the ordered genotype $\mathcal{A}_i\mathcal{A}_j$ by P_{ij}(= P_{ji}).

Since mating is at random, the genotype frequencies P_{ij} are in Hardy-Weinberg proportions. Let us suppose that selection acts solely through di erential viabilities and denote the tness (viability) of $\mathcal{A}_i\mathcal{A}_j$ individuals by $w_{ij} \geq 0$. We assume that the w_{ij} are constants, hence independent of time, population size, or genotype frequencies. In addition, we suppose $w_{ij} = w_{ji}$, as is usually the case. Then the frequency of $\mathcal{A}_i\mathcal{A}_j$ genotypes among adults that have survived selection is

$$P^*_{ij} = \frac{w_{ij}P_{ij}}{w} = \frac{w_{ij}p_i p_j}{w}\,,$$

where we have used (2.2). Here,

$$w = \sum_{ij} w_{ij}P_{ij} = \sum_{ij} w_{ij}p_i p_j = \sum_i w_i p_i \tag{2.3}$$

is the $mean\ fitness$ of the population and

$$w_i = \sum_j w_{ij}p_j \tag{2.4}$$

is the *marginal fitness* of allele $\mathcal{A}_i$. Both are functions of $p = (p_1, \ldots, p_I)^\top$.

Therefore, the frequency of $\mathcal{A}_i$ after selection is

$$p_i^* = \sum_j P_{ij}^* = p_i \frac{w_i}{w}. \tag{2.5}$$

Because of random mating, the allele frequency p_i' among zygotes of the next generation is also p_i^* (2.1), so that allele frequencies evolve according to the *selection equation*

$$p_i' = p_i \frac{w_i}{w}, \quad i \in \mathsf{I}. \tag{2.6}$$

This recurrence equation preserves the relation

$$\sum_i p_i = 1$$

and describes the evolution of allele frequencies at a single autosomal locus in a diploid population. We view the selection dynamics (2.6) as a (discrete) dynamical system on the simplex

$$\mathsf{S}_I = \left\{ p = (p_1, \ldots, p_I)^\top \in \mathbb{R}^I : p_i \geq 0 \text{ for every } i \in \mathsf{I}, \sum_i p_i = 1 \right\}.^3 \tag{2.7}$$

Although selection destroys Hardy-Weinberg proportions, random mating re-establishes them. Therefore, (2.6) is sufficient to study the evolutionary dynamics.

The right-hand side of (2.6) remains unchanged if every w_{ij} is multiplied by the same constant. This is very useful because it allows to rescale the fitness parameters according to convenience (also their number is reduced by one). Therefore, we will usually consider relative fitnesses and not absolute fitnesses.

Fitnesses are said to be *multiplicative* if constants v_i exist such that

$$w_{ij} = v_i v_j \tag{2.8}$$

for every i, j. Then $w_i = v_i v$, where $v = \sum_i v_i p_i$, and $w = v^2$. Therefore, (2.6) simplifies to

$$p_i' = p_i \frac{v_i}{v}, \quad i \in \mathsf{I}, \tag{2.9}$$

which can be solved explicitly because it is equivalent to the linear system $x_i' = v_i x_i$. It is easy to show that (2.9) also describes the dynamics of a haploid population if the fitness v_i is assigned to allele $\mathcal{A}_i$.

[3] Throughout, the superscript $^\top$ denotes vector or matrix transposition.

Fitnesses are said to be *additive* if constants v_i exist such that

$$w_{ij} = v_i + v_j \tag{2.10}$$

for every i, j. Then $w_i = v_i + v$, where $v = \sum_i v_i p_i$, and $w = 2v$. Although this assumption is important (it means absence of dominance; see Sect. 2.3), it does not yield an explicit solution of the selection dynamics.

Example 2.1. Selection is very efficient. We assume (2.8). Then the solution of (2.9) is

$$p_i(t) = \frac{p_i(0) v_i^t}{\sum_j p_j(0) v_j^t} \,. \tag{2.11}$$

Suppose that there are only two alleles, $\mathcal{A}_1$ and $\mathcal{A}_2$. If $\mathcal{A}_1$ is the wild type and $\mathcal{A}_2$ is a new beneficial mutant, we may set (without loss of generality!) $v_1 = 1$ and $v_2 = 1 + s$. Then we obtain from (2.11):

$$\frac{p_2(t)}{p_1(t)} = \frac{p_2(0)}{p_1(0)} \left(\frac{v_2}{v_1} \right)^t = \frac{p_2(0)}{p_1(0)} (1 + s)^t \,. \tag{2.12}$$

Thus, $\mathcal{A}_2$ increases exponentially relative to $\mathcal{A}_1$.

For instance, if $s = 0.5$, then after 10 generations the frequency of $\mathcal{A}_2$ has increased by a factor of $(1 + s)^t = 1.5^{10} \approx 57.7$ relative to $\mathcal{A}_2$. If $s = 0.05$ and $t = 100$, this factor is $(1 + s)^t = 1.05^{100} \approx 131.5$.

Therefore, *slight fitness differences may have a big long-term effect*. Also note that 100 generations are short on an evolutionary time scale.

An important property of (2.6) is that *mean fitness is nondecreasing along trajectories (solutions)*, i.e.,

$$w' = w(p') \geq w(p) = w \,, \tag{2.13}$$

and equality holds if and only if p is an equilibrium.[4]

Kingman (1961) provided a particularly elegant proof. As noted by Nagylaki (1977), (2.13) follows immediately from an inequality of Baum and Eagon (1967) by noting that (2.6) can be written as

$$p_i' = p_i \frac{\partial \bar{w}}{\partial p_i} \Big/ \sum_j p_j \frac{\partial \bar{w}}{\partial p_j}$$

because $\partial \bar{w} / \partial p_i = 2 w_i$.

[4] p is called an equilibrium, or fixed point, of the recurrence equation $p' = f(p)$ if $f(p) = p$. We use the term equilibrium point to emphasize that we consider an equilibrium that is a single point. The term equilibrium may also refer to a (connected) manifold of equilibrium points.

The statement (2.13) is closely related to *Fisher's Fundamental Theorem of Natural Selection*, which Fisher (1930) formulated as follows:

> "The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time."

For recent discussion, see Ewens (2011) and Bürger (2011).

In mathematical terms, (2.13) shows that w is a Lyapunov function. This has a number of important consequences. For instance, complex dynamical behavior such as limit cycles or chaos can be excluded. All trajectories approach the set of points $p \in S_I$ that are maxima of w. This is a subset of the set of equilibria. From (2.6) it is obvious that the equilibria are precisely the solutions of

$$p_i(w_i - w) = 0 \quad \text{for every } i\,. \tag{2.14}$$

We call an equilibrium internal, or fully polymorphic, if $p_i > 0$ for every i (all alleles are present). The I equilibria defined by $p_i = 1$ for some i are called monomorphic (only allele $\mathcal{A}_i$ is present).

The following result summarizes a number of important properties of the selection dynamics. For proofs and references to the original literature see Chap. I.9 in Bürger (2000).

Theorem 2.2. *1. If an isolated internal equilibrium exists, then it is uniquely determined.*

2. $\hat{p}$ is an equilibrium if and only if $\hat{p}$ is a critical point of the restriction of mean fitness $w(p)$ to the minimal subsimplex of S_I that contains the positive components of $\hat{p}$.

3. If the number of equilibria is finite, then it is bounded above by $2^I - 1$.

4. An internal equilibrium is asymptotically stable if and only if it is an isolated local maximum of w. Moreover, it is isolated if and only if it is hyperbolic (i.e., the Jacobian has no eigenvalues of modulus 1).

5. An equilibrium point is stable if and only if it is a local, not necessarily isolated, maximum of w.

6. If an asymptotically stable internal equilibrium exists, then every *orbit starting in the interior of S_I converges to that equilibrium.*

7. If an internal equilibrium exists, it is stable if and only if, counting multiplicities, the fitness matrix $W = (w_{ij})$ has exactly one positive eigenvalue.

8. If the matrix W has i positive eigenvalues, at least $(i-1)$ alleles will be absent at a stable equilibrium.

9. Every orbit converges to one of the equilibrium points (even if stable manifolds of equilibria exist).

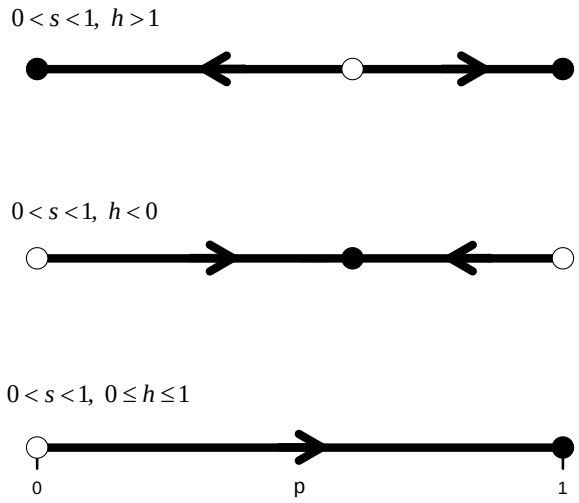

Figure 2.1: Convergence patterns for selection with two alleles.

2.3 Two alleles and the role of dominance

For the purpose of illustration, we work out the special case of two alleles. We write p and $1-p$ instead of p_1 and p_2. Further, we use relative tnesses and assume

$$w_{11} = 1\,,\ w_{12} = 1 - hs\,,\ w_{22} = 1 - s\,, \tag{2.15}$$

where s is called the *selection coefficient* and h describes the degree of dominance. We assume $s > 0$.

The allele $\mathcal{A}_1$ is called *dominant* if $h = 0$, partially dominant if $0 < h < \frac{1}{2}$, *recessive* if $h = 1$, and partially recessive if $\frac{1}{2} < h < 1$. *No dominance* refers to $h = \frac{1}{2}$. Absence of dominance is equivalent to additive tnesses (2.10). If $h < 0$, there is *overdominance* or *heterozygote advantage*. If $h > 1$, there is *underdominance* or *heterozygote inferiority*.

From (2.4), the marginal tnesses of the two alleles are

$$w_1 = 1 - hs + hsp \quad \text{and} \quad w_2 = 1 - s + s(1-h)p$$

and, from (2.3), the mean tness is

$$w = 1 - s + 2s(1-h)p - s(1-2h)p^2\,.$$

It is easily veri ed that the allele-frequency change from one generation to the next can

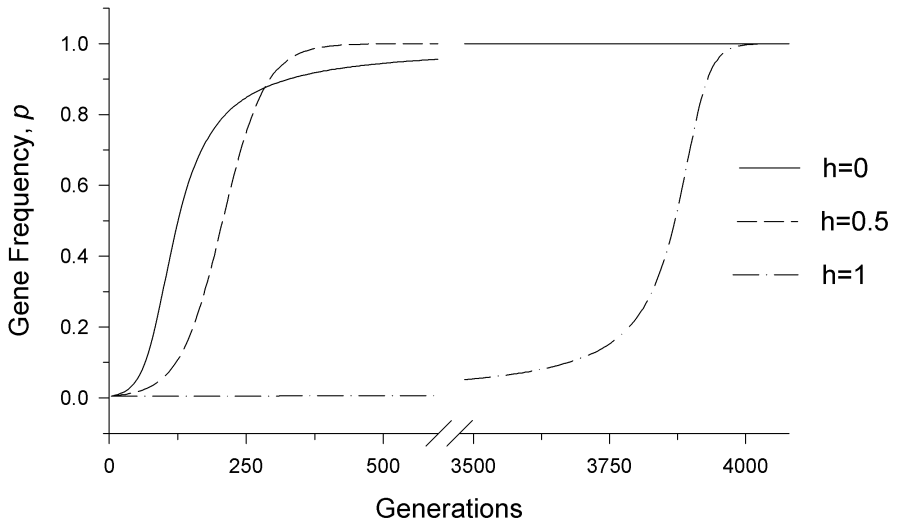

Figure 2.2: Selection of a dominant ($h = 0$, solid line), intermediate ($h = 1/2$, dashed), and recessive ($h = 1$, dash-dotted) allele. The initial frequency is $p_0 = 0.005$ and the selective advantage is $s = 0.05$. If the advantageous allele is recessive, its initial rate of increase is vanishingly small because the frequency p^2 of homozygotes is extremely low when p is small. However, only homozygotes are 'visible' to selection.

be written as

$$\Delta p = p' - p = \frac{p(1-p)}{2w}\frac{\mathrm{d}w}{\mathrm{d}p} \tag{2.16a}$$

$$= \frac{p(1-p)s}{w}\left[1 - h - (1-2h)p\right]. \tag{2.16b}$$

There exists an internal equilibrium if and only if $h < 0$ (overdominance) or $h > 1$ (underdominance). It is given by

$$\hat{p} = \frac{1-h}{1-2h}. \tag{2.17}$$

If dominance is intermediate, i.e., if $0 \le h \le 1$, then (2.16) shows that $\Delta p > 0$ if $0 < p < 1$, hence $p = 1$ is globally asymptotically stable.

If $h < 0$ or $h > 1$, we write (2.16) in the form

$$\Delta p = \frac{sp(1-p)}{w}(1-2h)(\hat{p} - p). \tag{2.18}$$

In the case of overdominance ($h < 0$), we have $0 < sp(1-p)(1-2h)/w < 1$ if $0 < p < 1$, hence $\hat{p}$ is globally asymptotically stable and convergence is monotonic. If $h > 1$, then the monomorphic equilibria $p = 0$ and $p = 1$ each are asymptotically stable and $\hat{p}$ is unstable.

The three possible convergence patterns are shown in Figure 2.1. Figure 2.2 demonstrates that the degree of (intermediate) dominance strongly a ects the rate of spread of an advantageous allele.

2.4 The continuous-time selection model

Most higher animal species have overlapping generations because birth and death occur continuously in time. This, however, may lead to substantial complications if one wishes to derive a continuous-time model from biological principles. By contrast, discrete-time models can frequently be derived straightforwardly from simple biological assumptions. If evolutionary forces are weak, a continuous-time version can usually be obtained as an approximation to the discrete-time model.

A rigorous derivation of the di erential equations describing gene-frequency change under selection in a diploid population with overlapping generations is a formidable task and requires a complex model involving age structure (see Nagylaki 1992, Chap. 4.10). Here, we simply state the system of di erential equations and justify it in an alternative way.

In a continuous-time model, the (*Malthusian*) tness m_{ij} of a genotype $\mathcal{A}_i\mathcal{A}_j$ is de ned as its birth rate minus its death rate. Then, the marginal tness of allele $\mathcal{A}_i$ is

$$m_i = \sum_j m_{ij} p_j \ ,$$

the mean tness of the population is

$$m = \sum_i m_i p_i = \sum_{i,j} m_{ij} p_i p_j \ ,$$

and the dynamics of allele frequencies becomes

$$\dot{p}_i = \frac{\mathrm{d}p_i}{\mathrm{d}t} = p_i(m_i - m) \ , \quad i \in \mathrm{I} \ .^{5} \tag{2.19}$$

This is the analogue of the discrete-time selection dynamics (2.6). Its state space is again the simplex S_I. The equilibria are obtained from the condition $\dot{p}_i = 0$ for every i. We note that (2.19) is a so-called *replicator equation* (see Hofbauer and Sigmund 1998).

Approximating the discrete-time model by the continuous-time model. First, observe that the difference equation (2.6) and the differential equation (2.19) have the same equilibria if we set

$$w_{ij} = 1 + s m_{ij} \quad \text{for every } i, j \in \mathrm{I} \ , \tag{2.20}$$

[5] Throughout, we use a dot, $\dot{}$, to indicate derivatives with respect to time.

where $s > 0$ is (sufficiently) small. This is obvious upon noting that (2.20) implies $w_i = 1 + sm_i$ and $\bar{w} = 1 + s\bar{m}$.

For weak selection the discrete model (2.6) can be approximated by the continuous model (2.19) as follows. Assume that w_{ij} is given by (2.20), rescale time according to $t = \lfloor \tau/s \rfloor$, where $\lfloor\ \rfloor$ denotes the closest smaller integer. Then s may be interpreted as generation length and, for $p_i(t)$ satisfying the difference equation (2.6), we write $\pi_i(\tau) = p_i(t)$. Then we obtain formally

$$\frac{\mathrm{d}\pi_i}{\mathrm{d}\tau} = \lim_{s\downarrow 0} \frac{1}{s} \left[\pi_i(\tau + s) - \pi_i(\tau)\right] = \lim_{s\downarrow 0} \frac{1}{s} \left[p_i(t+1) - p_i(t)\right] \ .$$

From (2.6) and (2.20), we obtain $p_i(t+1) - p_i(t) = sp_i(t)(m_i - \bar{m})/(1 + s\bar{m})$. Therefore, $\dot{\pi}_i = \pi_i(m_i - \bar{m})$ and $\Delta p_i \approx s\dot{\pi}_i = sp_i(m_i - \bar{m})$. We note that (2.6) is essentially the Euler scheme for (2.19).

The exact continuous-time model reduces to (2.19) only if the mathematically inconsistent assumption is imposed that Hardy-Weinberg proportions apply for every t which is generally not true. Under weak selection, however, deviations from Hardy-Weinberg decay to order $O(s)$ after a short period of time.

One of the advantages of models in continuous time is that they lead to di erential equations, and usually these are easier to analyze because the formalism of calculus is available. An example for this is that, in continuous time, (2.13) simpli es to

$$\bar{m} \geq 0\,. \tag{2.21}$$

This is *much* easier to prove than (2.13):

$$\bar{m} = 2\sum_{i,j} m_{ij} p_j p_i = 2\sum_i m_i p_i = 2\sum_i (m_i^2 - m^2) p_i = 2\sum_i (m_i - m)^2 p_i.$$

Remark 2.3. The allele-frequency dynamics (2.19) can be written as a (generalized) gradient system (Svirezhev 1972, Shahshahani 1979):

$$\dot{p} = G_p \ \mathrm{grad}\, \bar{m} = G_p \left(\frac{\partial \bar{m}}{\partial p_1}, \ldots, \frac{\partial \bar{m}}{\partial p_n} \right)^\top . \tag{2.22}$$

Here, $G_p = (g^{ij})$ is a quadratic (covariance) matrix, where

$$g^{ij} = \mathrm{Cov}(f_i, f_j) = \tfrac{1}{2} p_i (\delta_{ij} - p_j) \tag{2.23}$$

and

$$f_i(A_k A_l) = \begin{cases} 1 & \text{if } k = l = i\,, \\ \frac{1}{2} & \text{if } k \neq l \text{ and } k = i \text{ or } l = i\,, \\ 0 & \text{otherwise}\,. \end{cases} \tag{2.24}$$

Another equivalent formulation is the following covariance form:

$$\dot{p}_i = \mathrm{Cov}(f_i, m), \tag{2.25}$$

where m is interpreted as the random variable $m(A_k A_l) = m_{kl}$ (Li 1967). It holds under much more general circumstances (Price 1970, Lessard 1997).

3 The general migration-selection model

We assume a population of diploid organisms with discrete, nonoverlapping generations. This population is subdivided into demes. Selection acts within each deme through di erential viabilities. After selection adults migrate (disperse). After migration random mating occurs within each deme. We assume that the genotype frequencies are the same in both sexes (e.g., because the population is monoecious). We also assume that, in every deme, the population is so large that gene and genotype frequencies may be treated as deterministic, i.e., we ignore random genetic drift.

3.1 The recurrence equations

As before, we consider a single locus with I alleles $\mathcal{A}_i$ ($i \in$ I). Throughout, we use letters i, j to denote alleles, and greek letters α, β to denote demes. We write G = $\{1, \ldots, \ \}$ for the set of all demes. The presentation below is based on Chapter 6.2 of Nagylaki (1992).

We denote the frequency of allele $\mathcal{A}_i$ in deme α by $p_{i,\alpha}$. Therefore, we have

$$\sum_i p_{i,\alpha} = 1 \tag{3.1}$$

for every $\alpha \in$ G. Because selection may vary among demes, the tness (viability) $w_{ij,\alpha}$ of an $\mathcal{A}_i\mathcal{A}_j$ individual in deme α may depend on α. The marginal tness of allele $\mathcal{A}_i$ in deme α and the mean tness of the population in deme α are

$$w_{i,\alpha} = \sum_j w_{ij,\alpha} p_{j,\alpha} \quad \text{and} \quad w_\alpha = \sum_{i,j} w_{ij,\alpha} p_{i,\alpha} p_{j,\alpha}\,, \tag{3.2}$$

respectively.

Next, we describe migration. Let $m_{\alpha\beta}$ denote the probability that an individual in deme α migrates to deme β, and let $m_{\alpha\beta}$ denote the probability that an (adult) individual in deme α immigrated from deme β. The $\times$ matrices

$$M = (m_{\alpha\beta}) \quad \text{and} \quad M = (m_{\alpha\beta}) \tag{3.3}$$

are called the *forward* and *backward migration matrices*, respectively. Both matrices are *stochastic*, i.e., they are nonnegative and satisfy

$$\sum_\beta m_{\alpha\beta} = 1 \quad \text{and} \quad \sum_\beta m_{\alpha\beta} = 1 \quad \text{for every } \alpha\,. \tag{3.4}$$

Given the backward migration matrix and the fact that random mating within each demes does not change the allele frequencies, the allele frequencies in the next generation are

$$p'_{i,\alpha} = \sum_{\beta} m_{\alpha\beta} p^*_{i,\beta} \,, \tag{3.5a}$$

where

$$p^*_{i,\alpha} = p_{i,\alpha} \frac{w_{i,\alpha}}{w_\alpha} \tag{3.5b}$$

describes the change due to selection alone; cf. (2.6). These recurrence equations de ne a dynamical system on the -fold Cartesian product S_I^Γ of the simplex S_I. The investigation of this dynamical system, along with biological motivation and interpretation of results, is one of the main purposes of this lecture course.

The di erence equations (3.5) require that the backward migration rates are known. In the following, we derive their relation to the forward migration rates and discuss conditions when and how selection or migration do not change the deme proportions.

3.2 The relation between forward and backward migration rates

To derive this relation, we describe the life cycle explicitly. It starts with zygotes on which selection acts (possibly including population regulation). After selection adults migrate and usually there is population regulation after migration (for instance because the number of nesting places is limited). By assumption, population regulation does not change genotype frequencies. Finally, there is random mating and reproduction, which neither changes gene frequencies (Section 2.1) nor deme proportions. The respective proportions of zygotes, pre-migration adults, post-migration adults, and post-regulation adults in deme α are c_α, c^*_α, c^{**}_α, and c'_α:

Zygote	$\xrightarrow[\text{selection}]{}$	Adult	$\xrightarrow[\text{migration}]{}$	Adult	$\xrightarrow[\text{regulation}]{}$	Adult	$\xrightarrow[\text{reproduction}]{}$	Zygote
$c_\alpha \,,\, p_{i,\alpha}$		$c^*_\alpha \,,\, p^*_{i,\alpha}$		$c^{**}_\alpha \,,\, p'_{i,\alpha}$		$c'_\alpha \,,\, p'_{i,\alpha}$		$c'_\alpha \,,\, p'_{i,\alpha}$

Because no individuals are lost during migration, the following must hold:

$$c^{**}_\beta = \sum_{\alpha} c^*_\alpha m_{\alpha\beta} \,, \tag{3.6a}$$

$$c^*_\alpha = \sum_{\beta} c^{**}_\beta m_{\beta\alpha} \,. \tag{3.6b}$$

The (joint) probability that an adult is in deme α and migrates to deme β can be expressed in terms of the forward and backward migration rates as follows:

$$c^*_\alpha m_{\alpha\beta} = c^{**}_\beta m_{\beta\alpha}\,. \tag{3.7}$$

Inserting (3.6a) into (3.7), we obtain the desired connection between the forward and the backward migration rates:

$$m_{\beta\alpha} = \frac{c^*_\alpha m_{\alpha\beta}}{\sum_\gamma c^*_\gamma m_{\gamma\beta}}\,. \tag{3.8}$$

Therefore, if M is given, an *ansatz* for the vector $c^* = (c^*_1, \ldots, c^*_\Gamma)^\top$ in terms of $c = (c_1, \ldots, c_\Gamma)^\top$ is needed to compute M (as well as a hypothesis for the variation, if any, of c).

Two frequently used assumptions are the following.

1) *Soft selection*. This assumes that the fraction of adults in every deme is fixed, i.e.,

$$c^*_\alpha = c_\alpha \quad \text{for every } \alpha \in G. \tag{3.9}$$

This may be a good approximation if the population is regulated within each deme, e.g., because individuals compete for resources locally (Dempster 1955).

2) *Hard selection*. Following Dempster (1955), the fraction of adults will be proportional to mean fitness in the deme if the total population size is regulated. This has been called hard selection and is defined by

$$c^*_\alpha = c_\alpha w_\alpha / w\,, \tag{3.10}$$

where

$$w = \sum_\alpha c_\alpha w_\alpha \tag{3.11}$$

is the mean fitness of the total population.

Essentially, these two assumptions are at the extremes of a broad spectrum of possibilities. Soft selection will apply to plants; for animals many schemes are possible.

Under soft selection (3.9), (3.8) becomes

$$m_{\beta\alpha} = \frac{c_\alpha m_{\alpha\beta}}{\sum_\gamma c_\gamma m_{\gamma\beta}}\,. \tag{3.12}$$

As a consequence, if c is constant ($c' = c$), M is constant if and only if M is constant. If there is no population regulation after migration, then c will generally depend on time

because (3.6a) yields $c' = c^{**} = \mathbb{M}^\top c$. Therefore, the assumption of constant deme proportions, $c' = c$, will usually require that population control occurs after migration.

A migration pattern that does not change deme proportions ($c^{**}_\alpha = c^*_\alpha$) is called *conservative*. Under this assumption, (3.7) yields

$$c^*_\alpha \tilde{m}_{\alpha\beta} = c^*_\beta m_{\beta\alpha} \tag{3.13}$$

and, by stochasticity of M and $\mathbb{M}$, we obtain

$$c^*_\beta = \sum_\alpha c^*_\alpha \tilde{m}_{\alpha\beta} \quad \text{and} \quad c^*_\alpha = \sum_\beta c^*_\beta m_{\beta\alpha}\,. \tag{3.14}$$

If there is soft selection and the deme sizes are equal ($c^*_\alpha = c_\alpha \equiv$ constant), then $m_{\alpha\beta} = \tilde{m}_{\beta\alpha}$.

Remark 3.1. Conservative migration has two interesting special cases.

1) Dispersal is called *reciprocal* if the *number* of individuals that migrate from deme α to deme β equals the number that migrate from β to α:

$$c^*_\alpha \tilde{m}_{\alpha\beta} = c^*_\beta \tilde{m}_{\beta\alpha}\,. \tag{3.15}$$

If this holds for all pairs of demes, then (3.6a) and (3.4) immediately yield $c^{**}_\beta = c^*_\beta$. From (3.7), we infer $m_{\alpha\beta} = \tilde{m}_{\alpha\beta}$, i.e., the forward and backward migration matrices are identical.

2) A migration scheme is called *doubly stochastic* if

$$\sum_\alpha \tilde{m}_{\alpha\beta} = 1 \quad \text{for every } \alpha\,. \tag{3.16}$$

If demes are of equal size, then (3.6a) shows that $c^{**}_\alpha = c^*_\alpha$. Hence, with equal deme sizes a doubly stochastic migration pattern is conservative. Under soft selection, deme sizes remain constant without further population regulation. Hence, $m_{\alpha\beta} = \tilde{m}_{\beta\alpha}$ and M is also doubly stochastic.

Doubly stochastic migration patterns arise naturally if there is a periodicity, e.g., because the demes are arranged in a circular way. If we posit equal deme sizes and homogeneous migration, i.e., $\tilde{m}_{\alpha\beta} = \tilde{m}_{\beta-\alpha}$ so that migration rates depend only on distance, then the backward migration pattern is also homogeneous because $m_{\alpha\beta} = \tilde{m}_{\beta\alpha} = \tilde{m}_{\alpha-\beta}$ and, hence, depends only on $\beta - \alpha$. If migration is symmetric, $\tilde{m}_{\alpha\beta} = \tilde{m}_{\beta\alpha}$, and the deme sizes are equal, then dispersion is both reciprocal and doubly stochastic.

3.3 Important special migration patterns

We introduce three migration patterns that play an important role in the population genetical and ecological literature (see also Sect. 9.2).

Example 3.2. *Random outbreeding and site homing,* or the *Deakin* (1966) *model.* This model assumes that a proportion $\mu \in [0,1]$ of individuals in each deme leaves their deme and is dispersed randomly across all demes. Thus, they perform outbreeding whereas a proportion $1-\mu$ remains at their home site. If c_α^{**} is the proportion (of the total population) of post-migration adults in deme α, then the forward migration rates are defined by $m_{\alpha\beta} = \mu c_\beta^{**}$ if $\alpha \neq \beta$, and $m_{\alpha\alpha} = 1-\mu+\mu c_\alpha^{**}$. If $\mu = 0$, migration is absent; if $\mu = 1$, the *Levene* model is obtained (see below). Because this migration pattern is reciprocal (see below), $M = \mathcal{M}$ holds.

We shall always assume soft selection in the Deakin model, i.e., $c_\alpha^* = c_\alpha$. Thus, for a given (probability) vector $c = (c_1, \ldots, c_\Gamma)^\top$, the single parameter μ is sufficient to describe the migration pattern which, because $M = \mathcal{M}$, is given by

$$m_{\beta\alpha} = \begin{cases} \mu c_\alpha & \text{if } \alpha \neq \beta \\ 1-\mu+\mu c_\beta & \text{if } \alpha = \beta\,. \end{cases} \tag{3.17}$$

Proof. Migration in the Deakin model is reciprocal (3.15). From (3.7), we observe

$$m_{\beta\alpha} = \frac{c_\alpha^*}{c_\beta^{**}}\tilde{m}_{\alpha\beta} = \begin{cases} \mu c_\alpha^* & \text{if } \alpha \neq \beta \\ \dfrac{c_\beta^*}{c_\beta^{**}}(1-\mu)+\mu c_\beta^* & \text{if } \alpha = \beta\,. \end{cases} \tag{3.18}$$

From this we deduce

$$1 = \sum_\alpha m_{\beta\alpha} = \sum_{\alpha\neq\beta} \mu c_\alpha^* + \frac{c_\beta^*}{c_\beta^{**}}(1-\mu)+\mu c_\beta^* = \mu\cdot 1 + (1-\mu)\frac{c_\beta^*}{c_\beta^{**}}\,, \tag{3.19}$$

which immediately yields $c_\beta^{**} = c_\beta^*$ for every β provided $\mu < 1$. Therefore, we obtain $\tilde{m}_{\beta\alpha} = \mu c_\alpha^*$ if $\alpha \neq \beta$ and $c_\beta^*\tilde{m}_{\beta\alpha} = c_\beta^*\mu c_\alpha^* = c_\alpha^*\tilde{m}_{\alpha\beta}$, i.e., reciprocity. □

Example 3.3. *The Levene* (1953) *model* assumes soft selection and

$$m_{\alpha\beta} = c_\beta\,. \tag{3.20}$$

It has the property that $M = \mathcal{M}$. Thus, dispersing individuals are distributed randomly across all demes in proportion to the deme sizes. In particular, migration is independent of the deme of origin. We will treat the Levene model in considerable detail in Sect. 5.

We note that one could define the Levene model by $\tilde{m}_{\alpha\beta} = \mu_\beta$, where $\mu_\beta > 0$ are constants such that $\sum_\beta \mu_\beta = 1$. Then (3.8) yields $m_{\alpha\beta} = c_\beta^*$ for every $\alpha, \beta \in \mathsf{G}$. With soft selection, we get $m_{\alpha\beta} = c_\beta$. This is all we need if demes are regulated to constant proportions. But the proportions remain constant even without regulation, for (3.6a) gives $c'_\alpha = c_\alpha^{**} = \mu_\alpha$. This yields the usual interpretation $\mu_\alpha = c_\alpha$ (Nagylaki 1992, Sect. 6.3).

Example 3.4. In the *linear stepping-stone model* the demes are arranged in a linear order and individuals can reach only one of the neighboring demes. In the classical homogeneous version, the forward migration matrix is

$$\mathcal{M} = \begin{pmatrix} 1-m & m & 0 & \dots & 0 \\ m & 1-2m & m & & 0 \\ \vdots & & \ddots & & \vdots \\ 0 & & m & 1-2m & m \\ 0 & \dots & 0 & m & 1-m \end{pmatrix}. \tag{3.21}$$

We leave it to the reader to derive the backward migration matrix using (3.8). If all deme sizes are equal, then $M = \mathcal{M}$ and each deme exchanges a fraction m of the population with each of its neighboring demes. The stepping-stone model is an extreme case among migration patterns exhibiting *isolation by distance*, i.e., patterns in which the degree of migration diminishes with the distance from the parental deme. The stepping-stone model is also used as a starting point to derive the partial differential equations for selection and dispersal in continuous space (Nagylaki 1989). For generalizations and some specific results, see Sect. 9.2.1.

> Juvenile migration is of importance for many marine organisms and plants, where seeds disperse. It can be treated in a similar way as adult migration. Also models with both juvenile and adult migration have been studied. Some authors also investigated migration and selection in dioecious populations, as well as selection on X-linked loci (Nagylaki 1992, pp. 143, 144).

Unless stated otherwise, throughout these lecture notes we assume that the backward migration matrix M is constant, as is the case for soft selection if deme proportions and the forward migration matrix are constant. Then the recurrence equations (3.5) provide a self-contained description of the migration-selection dynamics. Hence, they are sufficient to study evolution for an arbitrary number of generations.

4 Protected polymorphism

Of central interest is the identification of conditions that guarantee the maintenance of genetic diversity. Often it is impossible to determine the equilibrium structure in detail because establishing existence and, even more so, stability or location of polymorphic equilibria is frequently unfeasible.

4.1 Basic concept and simple properties

Throughout this section we consider a single locus with two alleles. The number of demes, , is arbitrary. One says that there is a *protected polymorphism* (Prout 1968) if, no matter what the initial conditions are, the population cannot become monomorphic. Essentially, this requires to show that if an allele becomes very rare, then its frequency must increase. In general, a protected polymorphism is neither necessary nor su cient for the existence of a stable polymorphic equilibrium. For instance, on the one hand, if there is an internal limit cycle that attracts all solutions, then there is a protected polymorphism. On the other hand, if there are two internal equilibria, one asymptotically stable, the other unstable, then selection may remove one of the alleles if su ciently rare. A generalization of this concept to multiple alleles would correspond to the concept of permanence often used in ecological models (e.g., Hofbauer and Sigmund 1998).

Because we consider only two alleles, we can simplify the notation. We write $p_\alpha = p_{1,\alpha}$ for the frequency of allele $\mathcal{A}_1$ in deme α (and $1 - p_\alpha$ for that of $\mathcal{A}_2$ in deme α). Let $p = (p_1, \dots, p_\Gamma)^\top$ denote the vector of allele frequencies. Instead of using the tness assignments $w_{11,\alpha}$, $w_{12,\alpha}$, and $w_{22,\alpha}$, in the diallelic case it will be convenient to scale the tness of the three genotypes in deme α as follows

$$\begin{array}{ccc} \mathcal{A}_1\mathcal{A}_1 & \mathcal{A}_1\mathcal{A}_2 & \mathcal{A}_2\mathcal{A}_2 \\ x_\alpha & 1 & y_\alpha \end{array} \tag{4.1}$$

($x_\alpha, y_\alpha \geq 0$). Clearly, this can be achieved by setting $x_\alpha = w_{11,\alpha}/w_{12,\alpha}$ and $y_\alpha = w_{22,\alpha}/w_{12,\alpha}$.

With these tness assignments, one obtains

$$w_{1,\alpha} = 1 - p_\alpha + x_\alpha p_\alpha \quad \text{and} \quad w_\alpha = x_\alpha p_\alpha^2 + 2p_\alpha(1 - p_\alpha) + y_\alpha(1 - p_\alpha)^2 , \tag{4.2}$$

and the migration-selection dynamics (3.5) becomes

$$p^*_\alpha = p_\alpha w_{1,\alpha}/w_\alpha \tag{4.3a}$$

$$p'_\alpha = \sum_\beta m_{\alpha\beta} p^*_\beta . \tag{4.3b}$$

This can be viewed as a (discrete) dynamical system on $[0, 1]^\Gamma$.

We call allele $\mathcal{A}_1$ protected if it cannot be lost. Thus, it has to increase in frequency if rare. In mathematical terms this means that the monomorphic equilibrium $p = 0$ must be unstable. To derive a su cient condition for instability of $p = 0$, we linearize (4.3)

at $p = 0$. If $y_\alpha > 0$ for every α (which means that $\mathcal{A}_2\mathcal{A}_2$ is nowhere lethal), a simple calculation shows that the Jacobian of (4.3a),

$$D = \left(\frac{\partial p^*_\alpha}{\partial p_\beta}\right)\Bigg|_{p=0}, \tag{4.4}$$

is a diagonal matrix with (nonzero) entries $d_{\alpha\alpha} = y_\alpha^{-1}$. Because (4.3b) is linear, the linearization of (4.3) is

$$p' = Qp\,, \quad \text{where} \quad Q = MD\,, \tag{4.5}$$

i.e., $q_{\alpha\beta} = m_{\alpha\beta}/y_\beta$.

To obtain a simple criterion for protection, we assume that the descendants of individuals in every deme be able eventually to reach every other deme. Mathematically, the appropriate assumption is that M is irreducible. Then Q is also irreducible and it is nonnegative. Therefore, the Theorem of Perron and Frobenius (Appendix A.2) implies the existence of a uniquely determined eigenvalue $\lambda_0 > 0$ of Q such that $|\lambda| \le \lambda_0$ holds for all eigenvalues of Q. In addition, there exists a strictly positive eigenvector pertaining to λ_0 which, up to multiplicity, is uniquely determined. As a consequence,

$$\mathcal{A}_1 \textit{ is protected if } \ \lambda_0 > 1 \ \text{ and } \ \mathcal{A}_1 \textit{ is not protected if } \ \lambda_0 < 1 \tag{4.6}$$

(if $\lambda_0 = 1$, then stability cannot be decided upon linearization). This maximal eigenvalue satisfies

$$\min_\alpha \sum_\beta q_{\alpha\beta} \le \lambda_0 \le \max_\alpha \sum_\beta q_{\alpha\beta}\,, \tag{4.7}$$

with equality if and only if all the row sums are the same.

Example 4.1. Suppose that $\mathcal{A}_2\mathcal{A}_2$ is at least as fit as $\mathcal{A}_1\mathcal{A}_2$ in every deme and more fit in at least one deme, i.e., $y_\alpha \ge 1$ for every α and $y_\beta > 1$ for some β. Then $q_{\alpha\beta} = m_{\alpha\beta}/y_\beta \le m_{\alpha\beta}$ for every β. Because M is irreducible, there is no β such that $m_{\alpha\beta} = 0$ for every α. Therefore, the row sums $\sum_\beta q_{\alpha\beta} = \sum_\beta m_{\alpha\beta}/y_\beta$ in (4.7) are not all equal to one, and we obtain

$$\lambda_0 < \max_\alpha \sum_\beta q_{\alpha\beta} \le \max_\alpha \sum_\beta m_{\alpha\beta} = 1\,. \tag{4.8}$$

Thus, $\mathcal{A}_1$ is not protected, and this holds independently of the choice of the x_α, or $w_{11,\alpha}$.

It can be shown similarly that $\mathcal{A}_1$ is protected if $\mathcal{A}_1\mathcal{A}_2$ is favored over $\mathcal{A}_2\mathcal{A}_2$ in at least one deme and is nowhere less fit than $\mathcal{A}_2\mathcal{A}_2$. (For weak migration it is even sufficient that $\mathcal{A}_1\mathcal{A}_2$ is favored over $\mathcal{A}_2\mathcal{A}_2$ in at least one deme.)

One obtains the condition for protection of $\mathcal{A}_2$ if, in (4.6), $\mathcal{A}_1$ is replaced by $\mathcal{A}_2$ and λ_0 is the maximal eigenvalue of the matrix with entries $m_{\alpha\beta}/x_\beta$. Clearly, there is a protected polymorphism if both alleles are protected.

In the case of complete dominance the eigenvalue condition (4.6) cannot be satisfied. Consider, for instance, protection of $\mathcal{A}_1$ if $\mathcal{A}_2$ is dominant, i.e., $y_\alpha = 1$ for every α. Then $q_{\alpha\beta} = m_{\alpha\beta}$, $\sum_\beta q_{\alpha\beta} = \sum_\beta m_{\alpha\beta} = 1$, and $\lambda_0 = 1$. For a treatment of this case, see Nagylaki (1992, Chap. 6.2).

4.2 Two diallelic demes

It will be convenient to set

$$x_\alpha = 1 - r_\alpha \quad \text{and} \quad y_\alpha = 1 - s_\alpha\,, \tag{4.9}$$

where we assume $r_\alpha \leq 1$ and $s_\alpha \leq 1$ for $\alpha = 1$ and 2; cf. (4.1). We write the backward migration matrix as

$$M = \begin{pmatrix} 1 - m_1 & m_1 \\ m_2 & 1 - m_2 \end{pmatrix}, \tag{4.10}$$

where $0 < m_\alpha < 1$ for $\alpha = 1$ and 2.

We shall first derive the condition for protection of $\mathcal{A}_1$. The characteristic polynomial of Q is given by

$$\varphi(x) = (1-s_1)(1-s_2)x^2 - (2 - m_1 - m_2 - s_1 - s_2 + s_1m_2 + s_2m_1)x + 1 - m_1 - m_2\,. \tag{4.11}$$

This is convex and satisfies

$$\varphi(0) = 1 - m_1 - m_2 > 0\,, \quad \varphi(1) = s_1s_2(1-\kappa)\,, \tag{4.12a}$$

$$\varphi'(1) = (1-s_1)(m_2 - s_2) + (1-s_1)(m_1 - s_1)\,, \tag{4.12b}$$

where

$$\kappa = \frac{m_1}{s_1} + \frac{m_2}{s_2}\,. \tag{4.13}$$

By Example 4.1, $\mathcal{A}_1$ is not protected if $\mathcal{A}_1\mathcal{A}_2$ is less fit than $\mathcal{A}_2\mathcal{A}_2$ in both demes (more generally, if $s_1 \leq 0$, $s_2 \leq 0$, and $s_1 + s_2 < 0$). Of course, $\mathcal{A}_1$ will be protected if $\mathcal{A}_1\mathcal{A}_2$ is fitter than $\mathcal{A}_2\mathcal{A}_2$ in both demes (more generally, if $s_1 \geq 0$, $s_2 \geq 0$, and $s_1 + s_2 > 0$). Hence, we restrict attention to the most interesting case when $\mathcal{A}_1\mathcal{A}_2$ is fitter than $\mathcal{A}_2\mathcal{A}_2$ in one deme and less fit in the other, i.e., $s_1s_2 < 0$.

The Perron-Frobenius Theorem informs us that $\varphi(x)$ has two real roots. We have to determine when the larger one (λ_0) satisfies $\lambda_0 > 1$. From (4.11) and (4.12), we infer

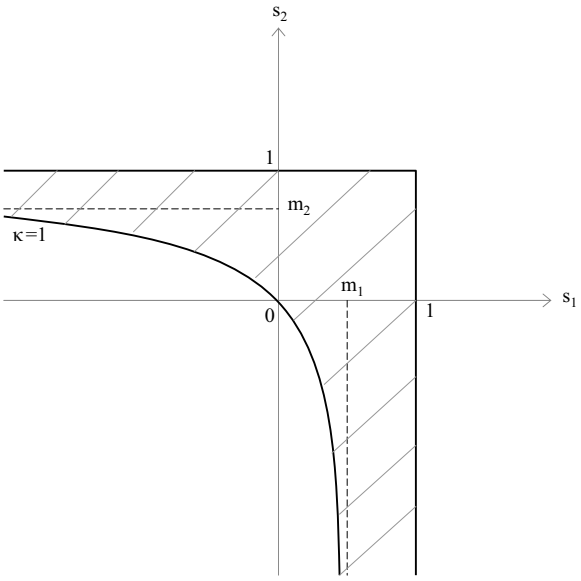

Figure 4.1: The region of protection of $\mathcal{A}_1$ (hatched). From Nagylaki and Lou (2008).

that this will be the case if and only if $\varphi(1) < 0$ or if $\varphi(1) > 0$ and $\varphi'(1) < 0$. It is straightforward to show that $\varphi(1) > 0$ and $\varphi'(1) < 0$ is never satis ed if $s_1 s_2 < 0$. Therefore, we conclude that, if $s_1 s_2 < 0$, then allele $\mathcal{A}_1$ is protected if

$$\kappa < 1\,; \tag{4.14}$$

cf. Bulmer (1972). It is not protected if $\kappa > 1$. Figure 4.1 displays the region of protection of $\mathcal{A}_1$ for given m_1 and m_2.

If there is no dominance ($r_\alpha = -s_\alpha$ and $0 < |s_\alpha| < 1$ for $\alpha = 1, 2$), then further simpli cation can be achieved. From the preceding paragraph the results depicted in Figure 4.2 are obtained. The region of a protected polymorphism is

$$_+ = \{(s_1, s_2) : s_1 s_2 < 0 \text{ and } |\kappa| < 1\}\ . \tag{4.15}$$

If $\mathcal{A}_1$ is recessive ($s_\alpha = 0$ and $r_\alpha \leq 1$ for $\alpha = 1{,}2$), the region of protected polymorphism is given by (Nagylaki 1992, Sect. 6.2)

$$\{(r_1, r_2) : r_1 r_2 < 0\,,\ \kappa^* < 1\,,\ \text{and } \kappa^{**} < 0\}\ , \tag{4.16}$$

where

$$\kappa^* = \frac{m_1}{r_1} + \frac{m_2}{r_2} \quad \text{and} \quad \kappa^{**} = m_2 r_1 + m_1 r_2\,. \tag{4.17}$$

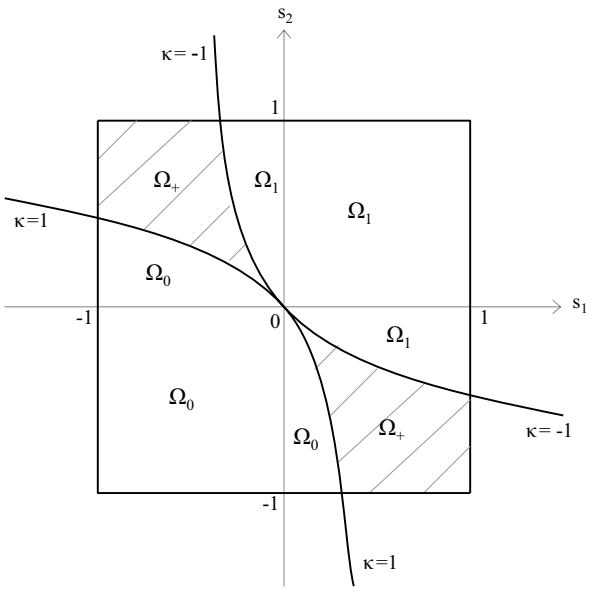

Figure 4.2: The regions of protection of $\mathcal{A}_2$ only (Ω_0), $\mathcal{A}_1$ only (Ω_1), and both $\mathcal{A}_1$ and $\mathcal{A}_2$ (Ω_+) in the absence of dominance. From Nagylaki and Lou (2008).

In a panmictic population, a stable polymorphism can not occur in the absence of overdominance. Protection of both alleles in a subdivided population requires that selection in the two demes is in opposite direction and su ciently strong relative to migration. Therefore, the study of the maintenance of polymorphism is of most interest if there is directional selection (intermediate dominance) in each deme in opposite direction, i.e.,

$$r_\alpha s_\alpha < 0 \text{ for } \alpha = 1, 2 \text{ and } s_1 s_2 < 0\,, \tag{4.18}$$

because then no polymorphism exists in a panmictic population.

Example 4.2. It is illuminating to study how the parameter region in which a protected polymorphism exists depends on the degree of dominance in the two demes. Figures 4.3 and 4.4 display the regions of protected polymorphism for two qualitatively different scenarios of dominance. In the first, the fitnesses are given by

$$\begin{array}{ccc} \mathcal{A}_1\mathcal{A}_1 & \mathcal{A}_1\mathcal{A}_2 & \mathcal{A}_2\mathcal{A}_2 \\ 1+s & 1+hs & 1-s \\ 1-as & 1-has & 1+as \end{array}\,, \tag{4.19}$$

thus, the degree of dominance is deme independent. In the second scenario, the fitnesses are given by

$$\begin{array}{ccc} \mathcal{A}_1\mathcal{A}_1 & \mathcal{A}_1\mathcal{A}_2 & \mathcal{A}_2\mathcal{A}_2 \\ 1+s & 1+hs & 1-s \\ 1-as & 1+has & 1+as \end{array}\,. \tag{4.20}$$

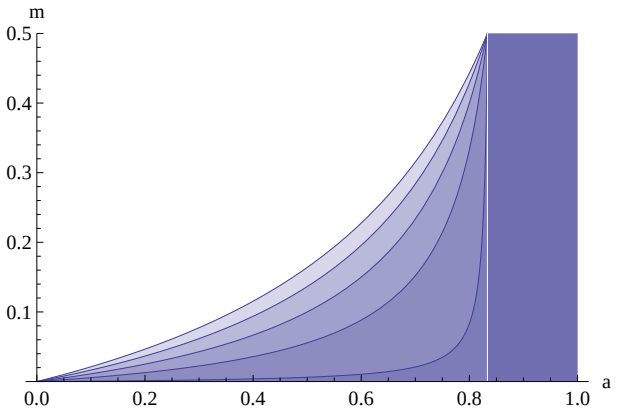

Figure 4.3: Influence of the degree of dominance on the region of protected polymorphism (shaded). The fitness scheme is given in (4.19), $s = 0.1$, and migration is symmetric, i.e., $m_1 = m_2 = m$. The values of h are -0.95, -0.5, 0, 0.5, 0.95 and correspond to the curves from left to right (light shading to dark shading). A protected polymorphism is maintained in the shaded area to the right of the respective curve. To the right of the white vertical line, a protected polymorphism exists for every m.

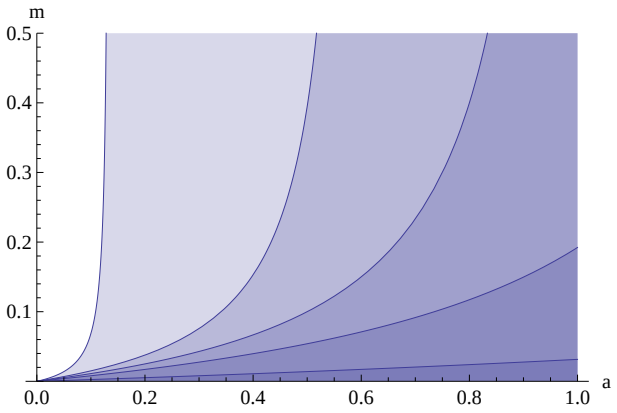

Figure 4.4: Influence of the degree of dominance on the region of protected polymorphism (shaded). The fitnesses are as in (4.20), $s = 0.1$, and migration is symmetric, i.e., $m_1 = m_2 = m$. The values of h are -0.75, -0.25, 0, 0.25, 0.75 and correspond to the curves from right to left (shading from dark to light!). A protected polymorphism is maintained in the shaded area to the right of the respective curve.

Hence, the fitter allele is always partially dominant. In both cases, a is a measure of the selection intensity in deme 2 relative to deme 1.

If, in (4.19), selection is sufficiently symmetric, i.e., $a > 1/(1+2s)$, there exists a protected polymorphism for every $h \leq 1$ and every $m \leq 1$. Otherwise, for given a, the critical migration rate m admitting a protected polymorphism decreases with increasing h because this increases the average fitness of $\mathcal{A}_1$. Given (4.20), increasing h greatly facilitates protected polymorphism because it leads to an increase of the average fitness of heterozygotes relative to the homozygotes.

Example 4.3. In the *Deakin model*, the condition (4.14) for protection of allele $\mathcal{A}_1$ becomes

$$\kappa = \mu \left(\frac{c_2}{s_1} + \frac{c_1}{s_2} \right) < 1 \tag{4.21}$$

(provided $s_1 s_2 < 0$). Therefore, for given s_1, s_2, and c_1, there is a critical value μ_0 such that allele $\mathcal{A}_1$ is protected if and only if $\mu < \mu_0$. This implies that for two diallelic demes a protected polymorphism is favored by a smaller migration rate.

Example 4.4. In the *Levene model*, the condition for a protected polymorphism is

$$\frac{c_2}{s_1} + \frac{c_1}{s_2} < 1 \quad \text{and} \quad \frac{c_2}{r_1} + \frac{c_1}{r_2} < 1\,. \tag{4.22}$$

We close this subsection with an example showing that the equilibrium structure can be quite complicated already with two alleles and two demes. Therefore, for general models insightful results beyond the existence or nonexistence of a protected polymorphism will not be easy to achieve.

Example 4.5. In the absence of migration, the recurrence equations for the allele frequencies p_1, p_2 in the two demes are two decoupled one-locus selection dynamics of the form (2.16). Therefore, if there is underdominance in each deme, the top convergence pattern in Figure 2.1 applies to each deme, i.e., the two monomorphic equilibria are asymptotically stable and the polymorphic equilibrium is unstable. As a consequence, in the absence of migration, the complete two-deme system has nine equilibria, four of which are asymptotically stable and the others are unstable. Karlin and McGregor (1972a) proved that under su ciently weak migration all nine equilibria are admissible and the four stable ones remain stable, whereas the other ve remain unstable. For increasing migration rate, several of these equilibria are extinguished by bifurcations. We shall encounter extensions of the perturbation theoretical results of Karlin and McGregor (1972b) in Sections 7, 10.4.

4.3 diallelic demes

The following result is useful for proving that an allele is protected. Let $I^{(n)}$ and $Q^{(n)}$ respectively designate the $n \times n$ unit matrix and the square matrix formed from the rst n rows and columns of Q.

Theorem 4.6 (Christiansen 1974). *If there exists a permutation of demes such that*

$$\det(I^{(n)} - Q^{(n)}) < 0 \tag{4.23}$$

for some n, where $1 \leq n \leq$, then $\mathcal{A}_1$ is protected.

The above theorem is sharp in the sense that if the inequality in (4.23) is reversed for every $n \leq$, then $\mathcal{A}_1$ is not protected. The proof applies a result of Wong (1967) to the criterion (4.6).

The simplest condition for protection is obtained from Theorem 4.6 by setting $n = 1$. Hence, $\mathcal{A}_1$ is protected if an α exists such that (Deakin 1972)

$$m_{\alpha\alpha}/y_\alpha > 1\,. \tag{4.24}$$

This condition assures that, when rare, the allele $\mathcal{A}_1$ increases in frequency in deme α even if this subpopulation is the only one containing the allele. The general condition in the above theorem assures that the allele increases in the n subpopulations if they are the only ones that contain it. Therefore, we get the following simple su cient condition for a protected polymorphism:

$$\text{There exist } \alpha \text{ and } \beta \text{ such that } m_{\alpha\alpha}/y_\alpha > 1 \text{ and } m_{\beta\beta}/x_\beta > 1. \tag{4.25}$$

Now we apply the above results to the Deakin model with an arbitrary number of demes.

Condition (4.25) becomes

$$\text{There exist } \alpha \text{ and } \beta \text{ such that } \frac{1-\mu(1-c_\alpha)}{y_\alpha} > 1 \text{ and } \frac{1-\mu(1-c_\beta)}{x_\beta} > 1. \tag{4.26}$$

A more elaborate and less stringent condition follows from Theorem 4.6.

Corollary 4.7 (Christiansen 1974). *For the Deakin model with ≥ 2 demes, the following is a sufficient condition for protection of $\mathcal{A}_1$. There exists a deme α such that*

$$1 - y_\alpha \geq \mu \tag{4.27}$$

or, if (4.27) *is violated in every deme* α*, then*

$$\mu \sum_{\alpha} \frac{c_\alpha}{\mu + y_\alpha - 1} > 1\,. \tag{4.28}$$

If (4.27) *is violated for every* α *and the inequality in* (4.28) *is reversed, then* A_1 *is not protected.*

First we prove the following:

Lemma 4.8. *Let* $T = \tilde{D} + B$*, where* $\tilde{D}$ *is an* $n \times n$ *diagonal matrix with elements* d_i *along the diagonal and* B *is an* $n \times n$ *matrix with identical rows,* $(b_1, \ldots, b_n)$*. Then*

$$\det(T) = \left(\prod_{i=1}^{n} d_i\right)\left(1 + \sum_{i=1}^{n} b_i/d_i\right)\,. \tag{4.29}$$

Proof.

$$\begin{aligned}
\det(T) &= \left(\prod_{i=1}^{n} d_i\right) \det \begin{pmatrix} 1+b_1/d_1 & b_2/d_2 & \cdots & b_n/d_n \\ b_1/d_1 & 1+b_2/d_2 & \cdots & b_n/d_n \\ \vdots & & \ddots & \vdots \\ b_1/d_1 & b_2/d_2 & \cdots & 1+b_n/d_n \end{pmatrix} \\
&= \left(\prod_{i=1}^{n} d_i\right) \det \begin{pmatrix} 1+b_1/d_1 & b_2/d_2 & \cdots & \cdots & b_n/d_n \\ -1 & 1 & 0 & \cdots & 0 \\ -1 & 0 & 1 & \cdots & \vdots \\ \vdots & \vdots & & \ddots & \\ -1 & 0 & \cdots & & 1 \end{pmatrix} \\
&= \left(\prod_{i=1}^{n} d_i\right)\left(1 + \sum_{i=1}^{n} b_i/d_i\right)\,.
\end{aligned}$$

□

Proof of Corollary 4.7. Let D and Q be as in (4.4) and (4.5). For the Deakin model, we have $M = (1-\mu)I + \mu C$, where C is the $\Gamma \times \Gamma$ with identical rows $(c_1, \ldots, c_\Gamma)$. Therefore, the matrix $I - Q = I - MD = I - (1-\mu)D - \mu CD$ has the form of T in Lemma 4.8, i.e.,

$$I - Q = \begin{pmatrix} 1-(1-\mu)/y_1 & & 0 \\ & \ddots & \\ 0 & & 1-(1-\mu)/y_\Gamma \end{pmatrix} - \mu \begin{pmatrix} c_1/y_1 & \cdots & c_\Gamma/y_\Gamma \\ \vdots & \ldots & \vdots \\ c_1/y_1 & \cdots & c_\Gamma/y_\Gamma \end{pmatrix}\,. \tag{4.30}$$

With the help of Lemma 4.8, we easily deduce

$$\det(I - Q) = \left[\prod_{\alpha}\left(1 - \frac{1-\mu}{y_\alpha}\right)\right]\left(1 - \sum_{\alpha} \frac{c_\alpha}{1-(1-y_\alpha)/\mu}\right)\,. \tag{4.31}$$

If $1 - y_\alpha \geq \mu$ for some α, then $\mathcal{A}_1$ is protected by (4.24). If $1 - y_\alpha < \mu$ for every α, then the product term in (4.31) is positive. Hence, by Theorem 4.6, the first term must be negative if $\mathcal{A}_1$ is to be protected. □

Corollary 4.7 can be extended to the inhomogeneous Deakin model, which allows for di erent homing rates, μ_α (Christiansen 1974; Karlin 1982, p. 182). This corollary extends the nding from two diallelic demes that a lower degree of outbreeding is favorable for protection of one or both alleles in the population. More precisely, we show the following.

Corollary 4.9. *If* $0 < \mu_1 \le \mu_2 \le 1$*, then allele* $\mathcal{A}_1$ *is protected for* μ_1 *if* μ_2 *satisfies Corollary 4.7.*

Proof. If condition (4.27) holds for μ_2, it clearly holds for μ_1. Now suppose that $1-y_\alpha < \mu_1$ for every α (hence $1 - y_\alpha < \mu_2$) and that μ_2 satisfies (4.28). This is equivalent to

$$\sum_\alpha \frac{c_\alpha(1-y_\alpha)}{\mu_1+y_\alpha-1}\,\frac{\mu_1+y_\alpha-1}{\mu_2+y_\alpha-1} = \sum_\alpha \frac{c_\alpha(1-y_\alpha)}{\mu_2+y_\alpha-1} > 0\,. \tag{4.32}$$

Because $(\mu_1 + y_\alpha - 1)/(\mu_2 + y_\alpha - 1) \ge \mu_1/\mu_2$ if and only if $y_\alpha > 1$, we obtain

$$\frac{\mu_1}{\mu_2}\sum_\alpha \frac{c_\alpha(1-y_\alpha)}{\mu_1+y_\alpha-1} \ge \sum_\alpha \frac{c_\alpha(1-y_\alpha)}{\mu_2+y_\alpha-1} > 0\,, \tag{4.33}$$

which proves our assertion. □

In general, it is not true that less migration favors the maintenance of polymorphism. For instance, if the amount of homing $(1 - \mu_\alpha)$ varies among demes (as in the inhomogeneous Deakin model), a protected polymorphism may be destroyed by decreasing one μ_α (Karlin 1982, p. 128).

Example 4.10. We apply Corollary 4.7 to the Levene model. Because, with $\mu = 1$, (4.27) can never be satis ed, $\mathcal{A}_1$ is protected from loss if the harmonic mean of the y_α is less than one, i.e., if (Levene 1953)

$$y^* = \left(\sum_\alpha \frac{c_\alpha}{y_\alpha}\right)^{-1} < 1\,. \tag{4.34a}$$

Analogously, allele $\mathcal{A}_2$ is protected if

$$x^* = \left(\sum_\alpha \frac{c_\alpha}{x_\alpha}\right)^{-1} < 1\,. \tag{4.34b}$$

Jointly, (4.34a) and (4.34b) provide a su cient condition for a protected polymorphism. If $y^* > 1$ or $x^* > 1$, then $\mathcal{A}_1$ or $\mathcal{A}_2$, respectively, is lost if initially rare.

If $\mathcal{A}_1$ is recessive everywhere ($y_\alpha = 1$ for every α), then it is protected if (Prout 1968)

$$x = \sum_\alpha c_\alpha x_\alpha > 1\,. \tag{4.35}$$

Therefore, a su cient condition for a protected polymorphism is

$$x^* < 1 < x\,. \tag{4.36}$$

5 The Levene model

This is a particularly simple model to examine the consequences of spatially varying selection for the maintenance of genetic variability. It can also be interpreted as a model of frequency-dependent selection. From the de nition (3.20) of the Levene model and equation (3.5a), we infer

$$p'_{i,\alpha} = \sum_{\beta} c_\beta p^*_{i,\beta}, \tag{5.1}$$

which is independent of α. Therefore, after one round of migration allele frequencies are the same in all demes, whence it is su cient to study the dynamics of the vector of allele frequencies

$$p = (p_1, \ldots, p_I)^\top \in \mathsf{S}_I\,. \tag{5.2}$$

The migration-selection dynamics (3.5) simpli es drastically and yields the recurrence equation

$$p'_i = p_i \sum_{\alpha} c_\alpha \frac{w_{i,\alpha}}{w_\alpha}\,, \quad \text{for every } i \in \mathsf{I}\,, \tag{5.3}$$

for the evolution of allele frequencies in the Levene model. Therefore, there is no population structure in the Levene model although the population experiences spatially varying selection. In particular, distance does not play any role. The dynamics (5.3) is also obtained if, instead of the life cycle in Section 3.2, it is assumed that adults form a common mating pool and zygotes are distributed randomly to the demes.

Remark 5.1. 1. In the *limit of weak selection*, the Levene model becomes equivalent with panmixia. Assume that there are constants $r_{ij,\alpha}$ such that

$$w_{ij,\alpha} = 1 + s r_{ij,\alpha}\,, \tag{5.4}$$

where $s > 0$ is a small number measuring the selection intensity. Set $t = \lfloor \tau/s \rfloor$ and define $\pi_i(\tau) = p(t)$, $r_{i,\alpha} = \sum_j r_{ij,\alpha}\pi_j$, and $\bar r_\alpha = \sum_i r_{i,\alpha}\pi_i$. Then (5.3) can be written as

$$\Delta p_i = p_i \sum_{\alpha} c_\alpha \frac{w_{i,\alpha} - \bar w_\alpha}{\bar w_\alpha} = p_i \sum_{\alpha} c_\alpha \frac{s(r_{i,\alpha} - \bar r_\alpha)}{1 + s\bar r_\alpha}\,. \tag{5.5}$$

Dividing by s and taking the limit $s \to 0$ produces

$$\dot\pi_i(\tau) = \pi_i \left(\sum_{\alpha} c_\alpha r_{i,\alpha} - \sum_{\alpha} c_\alpha \bar r_\alpha \right) = \pi_i(z_i - \bar z)\,, \tag{5.6}$$

which has the same structure as the selection dynamics in a randomly mating population because every $z_i = \sum_j z_{ij}\pi_j = \sum_j \sum_\alpha c_\alpha r_{ij,\alpha}\pi_j$ is linear in π and $\bar z = \sum_i z_i \pi_i$. Here,

$z_{ij} = \sum_\alpha c_\alpha r_{ij,\alpha}$ is the spatially averaged selection coefficient of $\mathcal{A}_i\mathcal{A}_j$. Therefore, the Levene model is of genuine interest only if selection is strong. (For arbitrary migration, the weak-selection limit generally does not lead to a panmictic dynamics.)

2. It can also be shown that the weak-selection limit for juvenile migration is panmixia (Nagylaki and Lou 2008).

3. If there is *hard selection* (3.10), the dynamics in the Levene model (with $m_{\alpha\beta} = c^*_\beta$) becomes

$$p_i' = p_i \frac{w_i}{\bar{w}} \quad (i \in \mathsf{I}), \text{ where } w_i = \sum_\alpha c_\alpha w_{i,\alpha}, \tag{5.7}$$

which is equivalent to the panmictic dynamics with fitnesses averaged over all demes. Therefore, no conceptually new behavior occurs. With two alleles, there exists a protected polymorphism if and only if the averaged fitnesses display heterozygous advantage. Interestingly, it is not true that the condition for protection of an allele under hard selection is always more stringent than under soft selection, although under a range of assumptions this is the case (see Nagylaki 1992, Sect. 6.3).

5.1 General results about equilibria and dynamics

We define

$$\bar{w} = \bar{w}(p) = \prod_\alpha w_\alpha(p)^{c_\alpha}, \tag{5.8}$$

which is the geometric mean of the mean fitnesses in single demes. Furthermore, we define

$$F(p) = \ln \bar{w}(p) = \sum_\alpha c_\alpha \ln w_\alpha(p). \tag{5.9}$$

Both functions will play a crucial role in our study of the Levene model.

From

$$\frac{\partial w_\alpha}{\partial p_i} = \frac{\partial}{\partial p_i} \sum_{i,j} p_i p_j w_{ij,\alpha} = 2 \sum_j p_j w_{ij,\alpha} = 2 w_{i,\alpha}, \tag{5.10}$$

we obtain

$$p_i' = p_i \sum_\alpha \frac{c_\alpha}{w_\alpha} \frac{1}{2} \frac{\partial w_\alpha}{\partial p_i} = \frac{1}{2} p_i \sum_\alpha c_\alpha \frac{\partial \ln w_\alpha}{\partial p_i} = \frac{1}{2} p_i \frac{\partial F(p)}{\partial p_i}. \tag{5.11}$$

Because $\sum_i p_i' = 1$, we can write (5.11) in the form

$$p_i' = p_i \frac{\partial \bar{w}(p)}{\partial p_i} \Big/ \sum_j p_j \frac{\partial \bar{w}(p)}{\partial p_j} = p_i \frac{\partial F(p)}{\partial p_i} \Big/ \sum_j p_j \frac{\partial F(p)}{\partial p_j}. \tag{5.12}$$

A simple exercise using Lagrange multipliers shows that the equilibria of (5.12), hence of (5.3), are exactly the critical points of $\bar{w}$, or F. Our aim is to prove the following theorem.

Theorem 5.2 (Li 1955; Cannings 1971; Nagylaki 1992, Sect. 6.3). *(a) Geometric-mean fitness satisfies* $\bar{w}(p) \geq 0$ *for every* $p \in S_I$, *and* $\bar{w}(p) = 0$ *if and only if* p *is an equilibrium of* (5.3). *The same conclusion holds for* F.

(b) The set $\quad$ *of equilibria is globally attracting, i.e.,* $p(t) \to \quad$ *as* $t \to \infty$. *If every point in* $\quad$ *is isolated, as is generic, then* $p(t)$ *converges to some* $\hat{p} \in \quad$. *Generically,* $p(t)$ *converges to a local maximum of* $\bar{w}$.

This is an important theoretical result because it states that in the Levene model no complex dynamical behavior, such as limit cycles or chaos, can occur. One immediate consequence of this theorem is

Corollary 5.3. *Assume the Levene model with two alleles. If there exists a protected polymorphism, then all trajectories converge to an internal equilibrium point.*

The proof of Theorem 5.2 is based on two important results, LaSalle's invariance principle (LaSalle 1976, p. 10) and the inequality of Baum and Eagon (1967). They are stated in the Appendix (Theorem A.2, Theorem A.5).

Outline of the proof of Theorem 5.2. (a) We assume that $c_\alpha \in \mathbb{Q}$ for every α. Then there exists $n \in \mathbb{N}$ such that $W = \tilde{w}^n$ is a homogeneous polynomial in p with nonnegative coefficients. From

$$\frac{\partial W}{\partial p_i} = n\tilde{w}^{n-1}\frac{\partial \tilde{w}}{\partial p_i}\,,$$

we infer

$$\frac{\partial W}{\partial p_i}\Big/\sum_j p_j\frac{\partial W}{\partial p_j} = \frac{\partial \tilde{w}}{\partial p_i}\Big/\sum_j p_j\frac{\partial \tilde{w}}{\partial p_j}\,.$$

From the inequality of Baum and Eagon; we infer immediately $W(p') > W(p)$ unless $p' = p$. Therefore, W and $\tilde{w}$ are (strict) Lyapunov functions. By a straightforward but tedious approximation argument, which uses compactness of S_I, it follows that $\tilde{w}$ is also a Lyapunov function if $c_\alpha \in \mathbb{R}$ (for details, see Nagylaki 1992, Sect. 6.3). This proves the first assertion in (a). The second follows immediately because the logarithm is strictly monotone increasing.

(b) The first statement is an immediate consequence of LaSalle's invariance principle. The second is obvious, and the third follows because $\tilde{w}$ is nondecreasing. (Note, however, that convergence to a maximum holds only generically because some trajectories may converge to saddle points. Moreover, because $\tilde{w}$ may also have minima and saddle points, the globally attracting set Λ may not be stable; only a subset of Λ is stable.) □

We will now derive a very useful criterion for the existence of a unique stable equilibrium. To this end, recall the de nition of $F(p) = \sum_\alpha c_\alpha \ln w_\alpha(p)$.

Lemma 5.4. *If* w_α *is concave for every* α, *then* F *is concave.*

Proof. Because the logarithm is a strictly monotone increasing and concave function, a simple estimate shows that $\ln w_\alpha$ is concave. Hence, F is concave. □

Theorem 5.5 (Nagylaki and Lou 2001). *If F is concave, there exists exactly one stable equilibrium (point or manifold) and it is globally attracting. If there exists an internal equilibrium, it is the global attractor.*

Proof. Concavity and the fact that $F \geq 0$ imply that if an internal equilibrium exists, it must be the global attractor.

Suppose now there exist two stable equilibrium points on the boundary of the simplex S_I. Because F is concave, F is constant on the line that joins them. If that line is on the boundary of S_I, then these two equilibrium points are elements of the same manifold of equilibria (on the boundary of S_I). If the line connecting them is an internal equilibrium, then the case treated above applies. □

If dominance is absent in every deme, there exist constants $v_{i,\alpha}$ such that

$$w_{ij,\alpha} = v_{i,\alpha} + v_{j,\alpha} \tag{5.13}$$

for every $i, j \in I$ and $\alpha \in G$, whence (3.2) yields

$$w_{i,\alpha} = v_{i,\alpha} + v_\alpha \quad \text{and} \quad w_\alpha = 2v_\alpha\,, \tag{5.14}$$

where

$$v_\alpha = \sum_i v_{i,\alpha} p_i\,. \tag{5.15}$$

A simple calculation shows that, without dominance the dynamics (5.3) simplifies to

$$p_i' = \tfrac{1}{2} p_i \left(1 + \sum_\alpha c_\alpha \frac{v_{i,\alpha}}{v_\alpha}\right) \quad (i \in I)\,. \tag{5.16}$$

Fitnesses are called *multiplicative* if there exist constants $v_{i,\alpha}$ such that

$$w_{ij,\alpha} = v_{i,\alpha} v_{j,\alpha} \tag{5.17}$$

for every $i, j \in I$ and $\alpha \in G$. Then (3.2) yields

$$w_{i,\alpha} = v_{i,\alpha} v_\alpha \quad \text{and} \quad w_\alpha = v_\alpha^2\,. \tag{5.18}$$

With multiplicative fitnesses, one obtains the haploid Levene model, i.e.,

$$p_i' = p_i \sum_\alpha c_\alpha v_{i,\alpha}/v_\alpha\,. \tag{5.19}$$

Theorem 5.6 (Nagylaki and Lou 2001). *The function F is concave in the following cases:*

(a) In every deme there is no dominance.

(b) In every deme fitnesses are multiplicative.

(c) In every deme a globally attracting internal equilibrium exists without migration (i.e., with the dynamics $p'_{i,\alpha} = p_{i,\alpha}w_{i,\alpha}/w_\alpha$).

Therefore, the conclusions of Theorem 5.5 apply in each of the cases.

Proof. (a) Without dominance, $w_\alpha = 2v_\alpha$ is linear in every deme.

(b) With multiplicative tnesses, $\ln w_\alpha = 2\ln v_\alpha$, which is concave because v_α is linear.

(c) If there is a globally attracting internal equilibrium in deme α when it is isolated, then the fact that $w_\alpha \geq 0$ implies that the quadratic w_α must be concave.

In all three cases, the assertion follows from Lemma 5.4. □

Remark 5.7. Theorems 5.5 and 5.6 hold for hard selection if we replace F by $\bar{w}$. For haploids, Strobeck (1979) proved uniqueness and asymptotic stability of an internal equilibrium.

Nagylaki and Lou (2006b) provide su cient conditions for the nonexistence of an internal equilibrium.

5.2 No dominance

Throughout this subsection, we assume no dominance, i.e., (5.13). For this important special case more detailed results can be proved than for general (intermediate) dominance, although, except under speci c assumptions (e.g., Theorem 4.2 in Nagylaki and Lou 2006b), equilibrium solutions cannot be determined explicitly. An interesting question to ask is: What determines the number of alleles that can be maintained at an equilibrium? If there is no dominance, there is a simple answer.

Theorem 5.8 (Nagylaki and Lou 2001). *Without dominance, the number of demes is a generic upper bound on the number of alleles present at equilibrium. Any neutral deme should not be counted in this bound.*

Proof. From (5.16) we conclude that, at an internal equilibrium $\hat{p}$,

$$\sum_\alpha c_\alpha \frac{v_{i,\alpha}}{\hat{v}_\alpha} = 1 \quad (i \in \mathrm{I}) \tag{5.20}$$

holds. The substitution

$$x_\alpha = c_\alpha / \hat{v}_\alpha\,, \quad \text{where } \hat{v}_\alpha = \sum_i v_{i,\alpha} \hat{p}_i\,, \tag{5.21}$$

linearizes (5.20):

$$\sum_\alpha v_{i,\alpha} x_\alpha = 1 \quad (i \in \mathrm{I})\,. \tag{5.22}$$

This is a system of I inhomogeneous linear equations for the unknowns x_α. Therefore, a solutions exists generically, i.e., for almost all tnesses and deme proportions, only if $I \leq$. (Note that even if there exists a solution (x_α), it does not necessarily give rise to a solution $\hat{p} \in \mathrm{S}_I$.)

The statement about neutral demes follows because in a neutral deme $v_{i,\alpha} = v_\alpha = 1$ for every i, hence $x_\alpha = c_\alpha$ holds. □

Remark 5.9. If in Theorem 5.8 general intermediate dominance is admitted, then there exists an open set of parameters for which any number of alleles can be maintained at an asymptotically stable equilibrium. Theorem 10.4 provides a much more general result.

Remark 5.10. Theorem 5.8 also holds for hard selection. A slight modification of the proof shows that it also holds for multiplicative fitnesses. In fact, Strobeck (1979) proved an analog of Theorem 5.8 for haploid species.

Example 5.11 (Nagylaki and Lou 2001)**.** We show that the upper bound established in Theorem 5.8 can be assumed if $= I$. Let $v_{i,\alpha} = u_i \delta_{i\alpha}$, where $u_i > 0$ and $\delta_{i\alpha}$ is the Kronecker delta. This means that allele $\mathcal{A}_i$ has tness u_i in deme i and tness 0 elsewhere. Hence, every allele is the best in one deme. Then (5.16) simpli es to

$$p_i' = \tfrac{1}{2} p_i \left(1 + \frac{u_i}{v_i}\right) = \tfrac{1}{2} p_i (1 + c_i/p_i) = \tfrac{1}{2}(p_i + c_i)\,. \tag{5.23}$$

This can be solved explicitly and yields $p_i(t) = c_i + (p_i(0) - c_i)(\frac{1}{2})^t \to c_i$ as $t \to \infty$.

In the formulation of Theorem 5.8, the word `generic' is essential. If and I are arbitrary and one assumes

$$w_{ij,\alpha} = 1 + r_{ij} g_\alpha \tag{5.24}$$

for (su ciently small) constants r_{ij} and g_α, it can be shown that an internal (hence globally attracting) manifold of equilibria exists for an open set of parameter combinations. This holds also for the additive case, when $r_{ij} = s_i + s_j$ (Nagylaki and Lou 2001).

Another interesting problem is to determine conditions when a speci c allele will go to xation. A simple and intuitive result is the following:

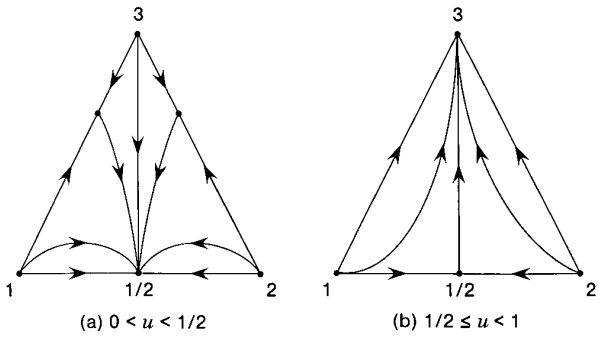

Figure 5.1: Phase portrait for the Levene model in Example 5.13 (Figure from Nagylaki and Lou 2001).

Theorem 5.12 (Nagylaki and Lou 2006b). *Suppose there exists $i \in \mathsf{I}$ such that*

$$\sum_{\alpha} c_\alpha \frac{v_{j,\alpha}}{v_{i,\alpha}} < 1 \tag{5.25}$$

for every $j \neq i$. Then $p_i(t) \to 1$ as $t \to \infty$.

A proof as well as additional results on the loss or fixation of alleles may be found in Nagylaki and Lou (2006b). The following example is based on a nice application of Theorem 5.6 and shows that migration may eliminate genetic variability.

Example 5.13 (Nagylaki and Lou 2001). We suppose two demes of equal size ($c_1 = c_2 = \frac{1}{2}$) and three alleles without dominance. The alleles $\mathcal{A}_1$ and $\mathcal{A}_2$ have extreme fitnesses and $\mathcal{A}_3$ is intermediate in both demes. More precisely, we assume $v_{1,1} = 1$, $v_{2,1} = 0$, $v_{3,1} = u$, and $v_{1,2} = 0$, $v_{2,2} = 1$, $v_{3,2} = u$, where $0 < u < 1$. Without migration, $\mathcal{A}_1$ is ultimately fixed in deme 1 and $\mathcal{A}_2$ is fixed in deme 2. We now establish that the Levene model evolves as sketched in Figure 5.1, i.e.,

$$p(t) \to \begin{cases} (\frac{1}{2}, \frac{1}{2}, 0) & \text{if } 0 < u < \frac{1}{2}\,, \\ (0, 0, 1) & \text{if } \frac{1}{2} \leq u < 1\,. \end{cases} \tag{5.26}$$

Because there is no dominance, Theorem 5.6 informs us that there can be only one stable equilibrium. Therefore, it is sufficient to establish asymptotic stability of the limiting equilibrium, which we leave as an easy exercise.

Following Nagylaki (2009a), we say there is deme-independent degree of intermediate dominance (DIDID) if

$$w_{ij,\alpha} = \vartheta_{ij} w_{ii,\alpha} + \vartheta_{ji} w_{jj,\alpha} \tag{5.27a}$$

holds for constants ϑ_{ij} such that

$$0 \leq \vartheta_{ij} \leq 1 \quad \text{and} \quad \vartheta_{ji} = 1 - \vartheta_{ij} \tag{5.27b}$$

for every α and every pair i, j. In particular, $\vartheta_{ii} = \frac{1}{2}$.

Obviously, DIDID covers complete dominance or recessiveness ($\vartheta_{ij} = 0$ or $= 1$ if $i \neq j$), and no dominance ($\vartheta_{ij} = \frac{1}{2}$), but not multiplicativity. We also note that DIDID includes the biologically important case of absence of genotype-by-environment interaction. In general, F is not concave under DIDID. However, Nagylaki (2009a, Theorem 3.2) proved that with DIDID the evolution of $p(t)$ is qualitatively the same as without dominance. Therefore, the conclusion of Theorem 5.5 holds, i.e., under DIDID there exists exactly one stable equilibrium (point or manifold) and it is globally attracting. If there exists an internal equilibrium, it is the global attractor. Moreover, the number of demes is a generic upper bound on the number of alleles that can segregate at an equilibrium (generalization of Theorem 5.8). Finally, the condition for loss of an allele in Theorem 5.12 has a simple generalization. For proofs and further results about DIDID consult Nagylaki (2009a).

Remark 5.14. For general migration, the dynamics under DIDID may differ qualitatively from that under no dominance. For instance, already in the diallelic continent-island model (i.e., one way migration), two asymptotically stable equilibria may coexist if there is DIDID (Nagylaki 2009a). Moreover, in two triallelic demes, a globally asymptotically stable internal equilibrium exists for an open set of parameters (Peischl 2010). In contrast, Theorem 2.4 in Nagylaki and Lou (2001) demonstrates that with arbitrary migration and no dominance, generically, the number of demes is an upper bound on the number of alleles that can be maintained at equilibrium. Thus, Peischl's result shows that this theorem does not generalize to DIDID.

5.3 Two alleles with dominance

Here, we specialize to two alleles but admit arbitrary dominance. We assume that fitnesses are given by (4.1). Our first result is an application of Theorem 5.5 and yields a further class of examples when a unique stable equilibrium exists.

Theorem 5.15 (Bürger 2009c). *For every α, let the fitnesses satisfy*

$$x_\alpha y_\alpha \leq 1 + (1 - y_\alpha)^2 \text{ and } y_\alpha \leq 1 \tag{5.28a}$$

or

$$x_\alpha y_\alpha \leq 1 + (1 - x_\alpha)^2 \text{ and } x_\alpha \leq 1\,. \tag{5.28b}$$

Then F is concave on $[0,1]$. Hence, there exists at most one internal equilibrium. If an internal equilibrium exists, it is globally asymptotically stable. If a monomorphic equilibrium is stable, then it is globally asymptotically stable.

Proof. We first prove that $\ln \bar{w}_\alpha$ is concave if and only if (5.28) is fulfilled. We have $\bar{w}_\alpha(p) = x_\alpha p^2 + 2p(1-p) + y_\alpha(1-p)^2$. Therefore, the second derivative of $\ln \bar{w}_\alpha$ is

$$\frac{d^2 \ln \bar{w}_\alpha(p)}{dp^2} = \frac{-2g_\alpha(p)}{\bar{w}_\alpha(p)^2}\,, \tag{5.29}$$

where

$$g_\alpha(p) = [1 - y_\alpha + p(x_\alpha + y_\alpha - 2)]^2 + 1 - x_\alpha y_\alpha\,. \tag{5.30}$$

Obviously, we have $g_\alpha(p) \geq 0$ for every p if $x_\alpha y_\alpha \leq 1$. Hence, $\ln \bar{w}_\alpha$ is concave if $x_\alpha y_\alpha \leq 1$, which is definitely the case if $x_\alpha + y_\alpha \leq 2$.

If $x_\alpha \geq 1$ and $y_\alpha \geq 1$ (and not both equal to 1), then $\ln \bar{w}_\alpha$ is not concave. Indeed, if $x_\alpha \geq y_\alpha$, then $x_\alpha y_\alpha \geq y_\alpha^2 \geq 1 + (1-y_\alpha)^2$ and at least one of the inequalities is strict because $x_\alpha > y_\alpha$ or $y_\alpha > 1$. Hence, we have $g_\alpha(0) = (1-y_\alpha)^2 + 1 - x_\alpha y_\alpha < 0$. If $y_\alpha \geq x_\alpha$, we obtain $g_\alpha(1) < 0$. In both cases, $\ln \bar{w}_\alpha$ is not concave.

Therefore, we can assume $x_\alpha + y_\alpha > 2$ and, without loss of generality, $y_\alpha \leq 1$. This implies that g_α is increasing on $[0,1]$ because

$$\frac{dg_\alpha(p)}{dp} = 2(x_\alpha + y_\alpha - 2)[1 - y_\alpha + p(x_\alpha + y_\alpha - 2)] \geq 0\,, \tag{5.31}$$

where equality can hold only if $p = 0$. Thus, $g_\alpha(p) \geq 0$ on $[0,1]$ if and only if $g_\alpha(0) \geq 0$. The latter, however, holds if and only if (5.28a) is satisfied. If $x_\alpha \leq 1$, then $g_\alpha(p) \geq 0$ on $[0,1]$ if and only if (5.28b) holds.

Now the conclusion follows from Lemma 5.4 and Theorem 5.5. □

Theorem 5.15 shows that the protection conditions (4.34) imply the existence of a globally asymptotically stable internal equilibrium if 5.28 holds. It generalizes Result I in Karlin (1977), who proved uniqueness of an internal equilibrium and global convergence under the assumption of *submultiplicative fitnesses*, i.e., if

$$x_\alpha y_\alpha \leq 1 \tag{5.32}$$

holds for every α (cf. Figure 5.2). His proof is based on a di erent method. Submultiplicative tnesses, hence tnesses satisfying (5.28), include a number of important cases: multiplicative tnesses (hence, selection on haploids), no dominance, partial or complete dominance of the tter allele, and overdominance.

Example 5.16. If there are two niches, no dominance, and tnesses given by $1 + s_\alpha$, 1, and $1 - s_\alpha$ ($s_1 s_2 < 0$), then (4.15) informs us that there is protected polymorphism if

$$|\kappa| < 1\,, \quad \text{where } \kappa = \frac{c_1}{s_2} + \frac{c_2}{s_1}\,. \tag{5.33}$$

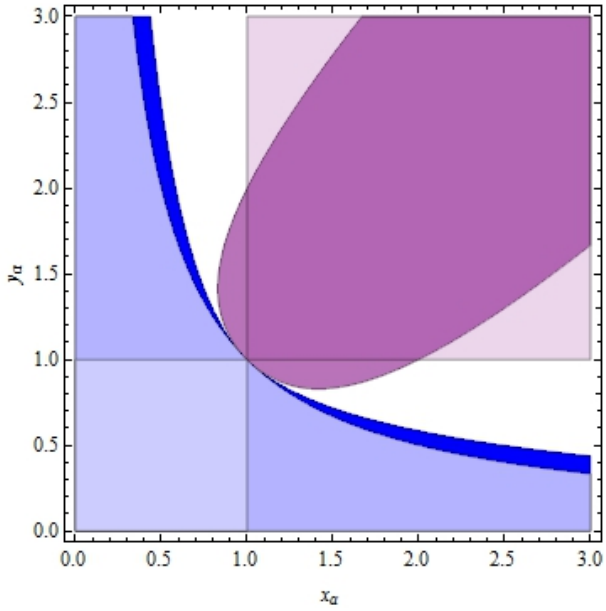

Figure 5.2: In the light blue regions fitnesses are submultiplicative, in the dark blue and light blue regions they satisfy (5.28). In the blue region(s), there exists a single stable equilibrium. In the purple region, fitnesses satisfy (5.35). There, both boundary equilibria are stable provided an internal equilibrium exists. In the light blue square there is overdominance, in the light purple square there is underdominance.

By Theorem 5.6 or 5.15 there is a unique, asymptotically stable equilibrium $\hat{p}$. A simple calculation yields $\hat{p} = (1-\kappa)/2$.

Example 5.17. If there are two niches and multiplicative tnesses given by $1/(1-s_\alpha)$, 1, and $1-s_\alpha$ ($s_1 s_2 < 0$), then there is a protected polymorphism if

$$0 < 1-\kappa < 1\,, \tag{5.34}$$

where κ is as above. The unique, asymptotically stable equilibrium is given by $\hat{p} = 1-\kappa$.

A partial converse to Theorem 5.15 is the following (stated without proof):

Theorem 5.18 (Karlin 1977, Result IA). *Suppose*

$$x_\alpha y_\alpha > 1 + \max\{(x_\alpha-1)^2, (y_\alpha-1)^2\} \quad \textit{for every } \alpha\,, \tag{5.35}$$

and there exists at least one internal equilibrium. Then both monomorphic equilibria are asymptotically stable and the internal equilibrium is unique.

Table 5.3 presents numerical results which demonstrate that stronger selection, submultiplicativity, and a higher number of demes all facilitate protected polymorphism in

the Levene model. These ndings agree with intuition. For instance, if an allele has su ciently low tness in just one deme, i.e., $c_\alpha/y_\alpha > 1$, the other allele is protected.

Γ	weak selection		moderate selection		strong selection	
	intdom	submult	intdom	submult	intdom	submult
2	0.094	0.185	0.115	0.271	0.220	0.332
3	0.124	0.262	0.162	0.416	0.357	0.516
4	0.138	0.310	0.190	0.512	0.460	0.636
10	0.158	0.468	0.270	0.788	0.787	0.917

Table 5.1: Proportion of protected polymorphism in the Levene model with intermediate dominance. Fitnesses of $\mathcal{A}_1\mathcal{A}_1$, $\mathcal{A}_1\mathcal{A}_2$, $\mathcal{A}_2\mathcal{A}_2$ are parameterized as $1+s_\alpha$, $1+h_\alpha s_\alpha$, $1-s_\alpha$. The data for weak selection are generated for the weak-selection limit (Remark 5.1). Then there is a protected polymorphism if and only if there is average overdominance, i.e., if $\sum_\alpha c_\alpha s_\alpha h_\alpha > |\sum_\alpha c_\alpha s_\alpha|$ holds. For moderate or strong selection, the conditions (4.34) were evaluated. In all cases, 10^6 parameter combinations satisfying $s_\alpha \in (-s, s)$, $h_\alpha \in (-1, 1)$, $c_\alpha \in (-1, 1)$ were randomly (uniformly) chosen, and the values c_α were normalized. For weak or strong selection, $s = 1$; for moderate selection, $s = 0.2$. For submultiplicative fitnesses (columns 'submult'), the 10^6 parameter combinations satisfy the additional constraint (5.32), which is reformulated as a condition for h_α. The columns 'intdom' contain the data for general intermediate dominance. The proportion of submultiplicative parameter combinations among all parameter combinations with intermediate dominance is $(1 - \frac{1}{2}\ln 2)^\Gamma \approx 0.653^\Gamma$.

So far, we derived su cient conditions for a unique (internal) equilibrium, but we have not yet considered the question of how many (stable) internal equilibria can coexist. This turns out to be a di cult question which was solved only recently for diallelic loci.

With tnesses given by (4.1), a simple calculation shows that the dynamics (5.3) can be written as

$$p = p(1-p)\sum_\alpha c_\alpha \frac{1 - y_\alpha + p(x_\alpha + y_\alpha - 2)}{x_\alpha p^2 + 2p(1-p) + y_\alpha(1-p)^2}\,. \tag{5.36}$$

Putting this on a common nominator, we see that the internal equilibria are the solutions of a polynomial in p of degree $2 \quad -1$. Thus, in principle, there can be up to $2 \quad -1$ internal equilibria. For two demes, Karlin (1977) provided a construction principle for obtaining three internal equilibria. It requires quite extreme tness di erences and that in both demes the less t allele is dominant.

By a clever procedure, Novak (2011) proved the following result:

Theorem 5.19. *The diallelic Levene model allows for any number $j \in \{1, 2, \ldots, 2 \quad -1\}$ of hyperbolic internal equilibria with any feasible stability configuration.*

His numerical results, which admit arbitrary dominance, show that the proportion of parameter space supporting more than equilibria becomes extremely small if > 2.

Because for arbitrary migration few general results are available, in the following sections we treat three limiting cases that are biologically important and amenable to mathematical analysis. These are weak selection and weak migration, weak migration (relative to selection), and weak selection (relative to migration). The first leads to the continuous-time migration model, the second to the so-called weak-migration limit, and the third to the strong-migration limit.

6 Migration and selection in continuous time

In this and the following sections, we study important limiting cases that are amenable to mathematical analysis than the general model. With the help of perturbation theory, such limiting cases can often be extended to an open subset of parameters of the full model.

We begin by assuming that both selection and migration are weak and approximate the discrete migration-selection dynamics (3.5) by a differential equation which is easier accessible. Accordingly, we assume

$$w_{ij,\alpha} = 1 + \epsilon r_{ij,\alpha} \quad \text{and} \quad m_{\alpha\beta} = \delta_{\alpha\beta} + \epsilon \mu_{\alpha\beta}\,, \tag{6.1}$$

where $r_{ij,\alpha}$ and $\mu_{\alpha\beta}$ are fixed for every $i, j \in I$ and every $\alpha, \beta \in G$, and $\epsilon > 0$ is sufficiently small. From (3.2) we deduce

$$w_{i,\alpha} = 1 + \epsilon r_{i,\alpha} \quad \text{and} \quad w_\alpha = 1 + \epsilon r_\alpha\,, \tag{6.2a}$$

where

$$r_{i,\alpha} = \sum_j r_{ij,\alpha} p_{j,\alpha} \quad \text{and} \quad r_\alpha = \sum_{i,j} r_{ij,\alpha} p_{i,\alpha} p_{j,\alpha}\,. \tag{6.2b}$$

To approximate the backward migration matrix M, note that (3.10) and (6.2a) imply that, for both soft and hard selection,

$$c_\alpha^* = c_\alpha + O(\epsilon) \tag{6.3}$$

as $\epsilon \to 0$. Substituting (6.1) and (6.3) into (3.8) leads to

$$m_{\alpha\beta} = \delta_{\alpha\beta} + \epsilon \mu_{\alpha\beta} + O(\epsilon^2) \tag{6.4}$$

as $\epsilon \to 0$, where

$$\mu_{\alpha\beta} = \frac{1}{c_\alpha} \left(c_\beta \mu_{\beta\alpha} - \delta_{\alpha\beta} \sum_\gamma c_\gamma \mu_{\gamma\alpha} \right)\,. \tag{6.5}$$

Because M is stochastic, we obtain $\mu_{\alpha\beta} \geq 0$ for every $\beta \neq \alpha$ and

$$\sum_{\beta} \mu_{\alpha\beta} = 0 \quad \text{for every } \alpha \in \quad . \tag{6.6}$$

As a simple consequence, $\mu_{\alpha\beta}$ satisfies the corresponding relations, i.e., $\mu_{\alpha\beta} \geq 0$ for every α and every $\beta \neq \alpha$, and

$$\sum_{\beta} \mu_{\alpha\beta} = 0 \quad \text{for every } \alpha \in \quad . \tag{6.7}$$

The final step in our derivation is to rescale time as in Sect. 2.4 by setting $t = \lfloor \tau/\epsilon \rfloor$ and $\pi_{i,\alpha}(\tau) = p_{i,\alpha}(t)$. Inserting all this into the difference equations (3.5) and expanding yields

$$\pi_{i,\alpha}(\tau + \epsilon) = \pi_{i,\alpha} \{1 + \epsilon[r_{i,\alpha}(\pi_{\cdot,\alpha}) - r_{\alpha}(\pi_{\cdot,\alpha})]\} + \epsilon \sum_{\beta} \mu_{\alpha\beta} \pi_{i,\beta} + O(\epsilon^2) \tag{6.8}$$

as $\epsilon \to 0$, where $\pi_{\cdot,\alpha} = (\pi_{1,\alpha}, \ldots, \pi_{I,\alpha})^{\top} \in S_I$. Rearranging and letting $\epsilon \to 0$, we arrive at

$$\frac{d\pi_{i,\alpha}}{d\tau} = \sum_{\beta} \mu_{\alpha\beta} \pi_{i,\beta} + \pi_{i,\alpha}[r_{i,\alpha}(\pi_{\cdot,\alpha}) - r_{\alpha}(\pi_{\cdot,\alpha})] \,. \tag{6.9}$$

Absorbing ϵ into the migration rates and selection coefficients and returning to $p(t)$, we obtain the slow-evolution approximation of (3.5),

$$\underline{p}_{i,\alpha} = \sum_{\beta} \mu_{\alpha\beta} p_{i,\beta} + p_{i,\alpha}[r_{i,\alpha}(p_{\cdot,\alpha}) - r_{\alpha}(p_{\cdot,\alpha})] \,. \tag{6.10}$$

We note that the migration and selection terms in (6.10) are decoupled. This is a general feature of many other slow-evolution limits (such as mutation and selection, or selection, recombination and migration).

It can be shown that (6.10) is also the slow-evolution approximation of the exact juvenile-migration model (Nagylaki and Lou 2008, Nagylaki 1992, pp. 143-144).

Akin (personal communication) has proved for three diallelic demes that Hopf bifurcation can produce unstable limit cycles. This precludes global convergence, though not generic convergence.

With multiple alleles, there are no general results on the dynamics of (6.10). For two alleles, we set $p_{\alpha} = p_{1,\alpha}$ and write (6.10) in the form

$$\underline{p}_{\alpha} = \sum_{\beta} \mu_{\alpha\beta} p_{\beta} + \varphi_{\alpha}(p_{\alpha}) \,. \tag{6.11}$$

Since $\mu_{\alpha\beta} \geq 0$ whenever $\alpha \neq \beta$, the system (6.11) is quasimonotone or cooperative, i.e., $\partial \underline{p}_{\alpha}/\partial p_{\beta} \geq 0$ if $\alpha \neq \beta$. As a consequence, (6.11) cannot have an exponentially stable

limit cycle. Moreover, if = 2, then every trajectory converges (Hirsch 1982; Hadeler and Glas 1983; see also Hofbauer and Sigmund 1998, p. 28). For the discrete-time model, convergence has not been demonstrated.

Example 6.1. Eyland (1971) provided a global analysis of (6.10) for the special case of two diallelic demes without dominance. As in Sect. 4.2, we assume that the tnesses of $\mathcal{A}_1\mathcal{A}_1$, $\mathcal{A}_1\mathcal{A}_2$, and $\mathcal{A}_2\mathcal{A}_2$ in deme α are 1 + s_α, 1, and 1 $-$ s_α, respectively, where $s_\alpha \neq 0$ (α = 1, 2). Moreover, we set $\mu_1 = \mu_{12} > 0$, $\mu_2 = \mu_{21} > 0$, and write p_α for the frequency of $\mathcal{A}_1$ in deme α. Then (6.10) becomes

$$\underline{p}_1 = \mu_1(p_2 - p_1) + s_1 p_1(1 - p_1)\,, \tag{6.12a}$$

$$\underline{p}_2 = \mu_2(p_1 - p_2) + s_2 p_2(1 - p_2)\,. \tag{6.12b}$$

The equilibria can be calculated explicitly. At equilibrium, $p_1 = 0$ if and only if $p_2 = 0$, and $p_1 = 1$ if and only if $p_2 = 1$. In addition, there may be an internal equilibrium point. We set

$$\sigma_\alpha = \frac{\mu_\alpha}{s_\alpha}\,, \quad \kappa = \sigma_1 + \sigma_2\,, \tag{6.13}$$

and

$$B = (1 - 4\sigma_1\sigma_2)^{1/2}\,. \tag{6.14}$$

The internal equilibrium exists if and only if $s_1 s_2 < 0$ and $|\kappa| < 1$; cf. (4.15). If $s_2 < 0 < s_1$, it is given by

$$\hat{p}_1 = \tfrac{1}{2}(1 + B) - \sigma_1 \quad \text{and} \quad \hat{p}_2 = \tfrac{1}{2}(1 - B) - \sigma_2\,. \tag{6.15}$$

It is straightforward to determine the local stability properties of the three possible equilibria. Gobal asymptotic stability follows from the results cited above about quasi-monotone systems. Let $p = (p_1, p_2)^\top$. Then allele $\mathcal{A}_1$ is eliminated in the region $_0$ in Figure 4.2, i.e., $p(t) \to (0, 0)$ as $t \to \infty$, whereas $\mathcal{A}_1$ is ultimately xed in the region $_1$. In $_+$, $p(t)$ converges globally to the internal equilibrium point $\hat{p}$ given by (6.15).

For the discrete-time dynamics (3.5) such a detailed analysis is not available. However, for important special cases, results about existence, uniqueness, and stability of equilibria were derived by Karlin and Campbell (1982). Some of them are treated in Sect. 9.1.2.

Finally, without proof, we present su cient conditions for global loss of an allele. In discrete time, such conditions are available only for the Levene model. For (6.10), however, general conditions were derived by Nagylaki and Lou (2007). Suppose that there exists $i \in$ I and constants γ_{ij} such that

$$\gamma_{ij} \geq 0\,, \quad \gamma_{ii} = 0\,, \quad \sum_j \gamma_{ij} = 1\,, \tag{6.16a}$$

and

$$\sum_j \gamma_{ij} r_{jk,\alpha} > r_{ik,\alpha} \tag{6.16b}$$

for every $\alpha \in$ G and every $k \in$ I.

Theorem 6.2 (Nagylaki and Lou 2007, Theorem 3.5 and Remark 3.7). *If the matrix* $(\mu_{\alpha\beta})$ *is irreducible and the conditions* (6.16) *are satisfied, then* $p_i(t) \to 0$ *as* $t \to \infty$ *whenever* $p_i(0) > 0$ *and* $p_j(0) > 0$ *for every* j *such that* $\gamma_{ij} > 0$.

If there is no dominance, constants $s_{i,\alpha}$ exist such that $r_{ij,\alpha} = s_{i,\alpha} + s_{j,\alpha}$ for every i, j, α. Then condition (6.16b) simplifies to

$$\sum_j \gamma_{ij} s_{j,\alpha} > s_{i,\alpha}\,, \tag{6.17}$$

and Theorem 6.2 applies.

To highlight one of the biological implications, we follow Remark 3.12 in Nagylaki and Lou (2007) and assume $\gamma_{i1} > 0$, $\gamma_{iI} > 0$, and $\gamma_{ij} = 0$ for $j = 2, \ldots, I-1$. Then (6.17) becomes

$$\gamma_{i1} s_{1,\alpha} + \gamma_{iI} s_{I,\alpha} > s_{i,\alpha} \tag{6.18}$$

for every α, and the theorem shows that $p_i(t) \to 0$ as $t \to \infty$ for $i = 2, \ldots, I-1$. If, in addition to (6.18), we assume that

$$\min(s_{1,\alpha}, s_{I,\alpha}) < s_{i,\alpha} < \max(s_{1,\alpha}, s_{I,\alpha}) \tag{6.19}$$

for $i = 2, \ldots, I-1$ and every α, then every allele $\mathcal{A}_i$ with $1 < i < I$ is intermediate in every deme, and $\mathcal{A}_1$ and $\mathcal{A}_I$ are extreme. Thus, Theorem 6.2 implies that all intermediate alleles are eliminated. This conclusion can be interpreted as the elimination of generalists by specialists, and it can yield the increasing phenotypic differentiation required for parapatric speciation (cf. Lou and Nagylaki 2002 for an analogous result and discussion in the context of diffusion models). If $s_{1,\alpha} - s_{I,\alpha}$ changes sign among demes, so that every allele is the fittest in some deme(s) and the least fit in the other(s), then both alleles may be maintained.

An other application of Theorem (6.2) is the following. If in every deme the homozygotes have the same fitness order and there is strict heterozygote intermediacy, then the allele with the greatest homozygous fitness is ultimately fixed (Remark 3.20 in Nagylaki and Lou 2007).

7 Weak migration

If migration is sufficiently weak relative to selection, then properties of the dynamics can be inferred by perturbation techniques from the well-understood case of a finite number of isolated demes in which there is selection and random mating.

To study weak migration, we assume

$$m_{\alpha\beta} = \delta_{\alpha\beta} + \epsilon\mu_{\alpha\beta}\,, \tag{7.1}$$

where $\mu_{\alpha\beta}$ is fixed for every α, β, and $\epsilon > 0$ is sufficiently small. Because M is stochastic, we obtain (cf. Section 6)

$$\mu_{\alpha\beta} \geq 0 \text{ for every } \beta \neq \alpha \quad \text{and} \quad \sum_{\beta} \mu_{\alpha\beta} = 0 \text{ for every } \alpha \in \quad . \tag{7.2}$$

If there is no migration ($\epsilon = 0$), then the dynamics in each deme reduces to the pure selection dynamics

$$p'_{i,\alpha} = p_{i,\alpha}\frac{w_{i,\alpha}}{w_\alpha}\,. \tag{7.3}$$

Because (7.3) is defined on the Cartesian product S_I^Γ, it may exhibit a richer equilibrium and stability structure than the panmictic selection dynamics. This was already illustrated by Example 4.5. We present two additional examples.

Example 7.1. We consider = 2 demes and $I \geq 2$ alleles. Let us decompose the set I of alleles into two nonempty subsets I_1 and I_2 such that $I = I_1 \cup I_2$ and $I_1 \cap I_2 = \emptyset$. Now assume that in each deme the selection scheme is such that, without migration, an asymptotically stable equilibrium $\hat{p}$ exists that has the following properties:

$$\hat{p}_{i,\alpha} > 0 \quad \text{if } i \in I_\alpha\,, \tag{7.4a}$$

$$\hat{p}_{i,\alpha} = 0 \quad \text{otherwise} \tag{7.4b}$$

(this may require overdominance). This means that in deme 1 the alleles in I_1 are present at equilibrium, and in deme 2 the alleles in I_2 are present. In the population as a whole, all alleles are present at $\hat{p}$. We can expect that this property persists under small perturbations, i.e., for arbitrary, but sufficiently small, migration rates. Indeed, this can be proved if the unperturbed equilibrium is hyperbolic.

Example 7.2. Let ≥ 2, $I \geq 2$, and assume no dominance. Then, generically, in every deme one allele is the best (in the sense that it has highest homozygote fitness). It is easy

to show that in every deme the best allele will ultimately become fixed. Therefore, in the whole population, the number of alleles present at the (unique) stable equilibrium cannot be larger than the number of demes. We will extend this result to weak migration and intermediate dominance.

We note that for (7.3), hyperbolicity is a generic property (Appendix A in Nagylaki et al. 1999). An internal equilibrium is hyperbolic if and only if it is isolated (Lemma 3.2 in Nagylaki and Lou 2006a). The following is the main result of this section. Below, we outline its proof and discuss some applications.

Theorem 7.3 (Nagylaki and Lou 2007, Theorem 4.1). *Suppose that every equilibrium of* (7.3) *is hyperbolic, that* (7.1) *holds, and that* $\epsilon > 0$ *is sufficiently small.*

(a) The set of equilibria $_0 \subset S_I^\Gamma$ *of* (7.3) *contains only isolated points, as does the set of equilibria* $_\epsilon \subset S_I^\Gamma$ *of* (3.5). *As* $\epsilon \to 0$, *each equilibrium in* $_\epsilon$ *converges to the corresponding equilibrium in* $_0$.

(b) In the neighborhood of each asymptotically stable equilibrium in $_0$, *there exists exactly one equilibrium in* $_\epsilon$, *and it is asymptotically stable. In the neighborhood of each unstable internal equilibrium in* $_0$, *there exists exactly one equilibrium in* $_\epsilon$, *and it is unstable. In the neighborhood of each unstable boundary equilibrium in* $_0$, *there exists at most one equilibrium in* $_\epsilon$, *and if it exists, it is unstable.*

(c) Every solution $p(t)$ *of* (3.5) *converges to one of the equilibrium points in* $_\epsilon$.

The perturbation results in (a) and (b) are essentially due to Karlin and McGregor (1972a,b). The proof of (c), which also yields (a) and (b), is a simplification of that of Theorem 2.3 in Nagylaki et al. (1999) and is based on quite deep results. To outline the proof, we need some preparation.

We consider a family of maps (difference equations) that depends on a parameter ϵ,

$$x' = f(x, \epsilon)\,, \tag{7.5}$$

where $x \in X \subseteq \mathbb{R}^n$ (X compact and convex) and $\epsilon \in E \subseteq \mathbb{R}^k$ (E open). We assume that $\hat{x}$ is a fixed point of (7.5) if $\epsilon = \epsilon_0$ and that the Jacobian $f'(\hat{x}, \epsilon_0)$ of f evaluated at $(\hat{x}, \epsilon_0)$ exists and is continuous. Furthermore, we posit that $\hat{x}$ is a hyperbolic equilibrium. If we define the function

$$F(x, \epsilon) = f(x, \epsilon) - x\,, \tag{7.6}$$

then $F(\hat{x}, \epsilon_0) = 0$ and the Jacobian $F'(\hat{x}, \epsilon_0)$ is continuous and nonsingular (by hyperbolicity of $\hat{x}$). Therefore, the implicit function theorem shows that there exists an open

neighborhood U of ϵ_0 and a function ϕ : U $\to$ X such that $\phi(\epsilon_0)$ = $\hat{x}$ and $F(\phi(\epsilon), \epsilon)$ = 0 for $\epsilon \in$ U, hence

$$f(\phi(\epsilon), \epsilon) = \phi(\epsilon)\,. \tag{7.7}$$

Hence, for every $\epsilon \in$ U, i.e., for ϵ close to ϵ_0, (7.5) has a uniquely determined fixed point $\hat{x}_\epsilon = \phi(\epsilon)$ close to $\hat{x}$.

With the help of the Hartman-Grobman theorem, it can be shown that the stability properties of the perturbed fixed points $\hat{x}_\epsilon$ are the same as those of the unperturbed, $\hat{x}$. The reason is that if an equilibrium is hyperbolic, this property persists under small perturbations (the Jacobian changes continuously if parameters change continuously); see also Theorem 4.4 in Karlin and McGegor (1972b). The extension of this argument to finitely many hyperbolic equilibria is evident.

Although hyperbolic equilibria change continuously under small perturbations, limit sets of trajectories do not: they can explode. Thus, perturbations could introduce `new' limit sets away from the hyperbolic equilibria. What has good properties under perturbations is the set of *chain-recurrent points* introduced by Conley (1978).

Let X be a compact set with metric d and let f : X $\to$ X be a continuous map. A point $x \in$ X is called *chain recurrent* (with respect to f) if, for every $\delta > 0$, there exists a finite sequence $x_0 = x, x_1, \ldots, x_{r-1}, x_r = x$ (often called a δ-pseudo-orbit) such that $d(f(x_m), x_{m+1}) < \delta$ for m = 0, 1, ..., $r-1$. The set of chain-recurrent points contains the limit sets of all orbits. In contrast to these limit sets, which need not change continuously under small perturbations, the set of chain-recurrent points has good properties under perturbations (Akin 1993, p. 244).

Outline of the proof of Theorem 7.3. (a) and (b) follow from the implicit function theorem and the Hartman-Grobman theorem. That asymptotically stable boundary equilibria remain in the state space follows from Brouwer's fixed point theorem (for details, see Karlin and McGgregor 1972, especially Theorem 4.4).

(c) Let

$$\mathrm{F} = \{p \in \mathrm{S}_I^\Gamma : p_{i,\alpha}(w_{i,\alpha} - w_\alpha) = 0 \ \forall i \in \mathrm{I}, \forall \alpha \in \ \} \tag{7.8}$$

denote the set of equilibria of (7.3). Then, within in each deme, $w_\alpha \geq 0$ with equality only at equilibrium; cf. (2.13). Hence,

$$w(p) = \sum_\alpha w_\alpha(p_{\cdot,\alpha}) \tag{7.9}$$

satis es $w(p) \geq 0$ with $w(p) = 0$ if and only if $p \in F$. Because, on F, w takes only nitely many values, Theorem 3.14 in Akin (1993) implies that the chain-recurrent points of (7.3) are exactly the equilibria.

Now we can follow the proof of Theorem 2.3 in Nagylaki et al. (1999) almost verbally. Because the set of chain-recurrent points consists only of hyperbolic equilibria, this is also true for small C^1 perturbations of the dynamics (see, e.g., Akin 1993, p. 244). Indeed, as an immediate consequence of the de nition of chain recurrence, it follows that the chain-recurrent set of (7.3) changes in an upper semicontinuous way with ϵ. In particular, the chain-recurrent set for $\epsilon > 0$ is contained in the union of the δ-neighborhoods of the equilibria for $\epsilon = 0$, with $\delta \to 0$ for $\epsilon \to 0$. By the implicit function theorem and the openness of hyperbolicity (Hartman-Grobman theorem), if $\epsilon > 0$ is small, then the maximal invariant sets in those neighborhoods are hyperbolic equilibria. Hence, for small ϵ, the chain-recurrent set consists only of nitely many equilibria, which implies convergence of all trajectories. □

Remark 7.4. Boundary equilibria that are unstable in the absence of migration, can disappear under weak migration because the move outside S_I^Γ. A simple example is overdominance in two diallelic demes: the unstable zero-migration equilibria $(p_{1,1}, p_{1,2}) = (1, 0)$ and $(p_{1,1}, p_{1,2}) = (0, 1)$ do not survive perturbation. Indeed, if $\epsilon > 0$, the perturbation of $(1, 0)$ must have the form $(1 - \epsilon z_1, \epsilon z_2)$. If the tnesses of the genotypes are as in (4.1) and the migration rates are $m_{12} = \epsilon m_1$ and $m_{21} = \epsilon m_2$, then straightforward calculations show that this equilibrium is given by

$$z_1 = -\frac{x_1 m_1}{1 - x_1} \quad \text{and} \quad z_2 = -\frac{y_2 m_2}{1 - y_2},$$

which is not in $[0, 1] \times [0, 1]$ if there is overdominance, i.e., if $x_\alpha < 1$ and $y_\alpha < 1$.

Remark 7.5. In the absence of migration, mean tness is monotone increasing in each deme (except at the equilibria). Therefore, by continuity, $w(p) = \sum_\alpha w_\alpha(p_{\cdot,\alpha}) > 0$ for su ciently small ϵ if p is bounded away from F. If p is close to F, mean tness may decrease. As an example assume two diallelic demes with overdominance and (stable) equilibria $\hat{p}_{\cdot,1}$ and $\hat{p}_{\cdot,2}$ with $\hat{p}_{\cdot,1} \neq \hat{p}_{\cdot,2}$. Suppose that in some generation $p_{\cdot,\alpha} = \hat{p}_{\cdot,\alpha}$ holds for $\alpha = 1, 2$. Since $w(p)$ is maximized at $\hat{p}$, which, with migration, is an equilibrium only if $\hat{p}_{\cdot,1} = \hat{p}_{\cdot,2}$, we see that $w(p') < w(p)$.

As another application of Theorem 7.3, we study how many alleles can be maintained at an asymptotically stable equilibrium under weak migration. First we prove a simple result for a single deme. (For more general results, see Sect. 2 in Nagylaki and Lou 2006a.)

Proposition 7.6. *Let* = 1 *and assume that the alleles are ordered such that* $w_{ii} \geq w_{i+1,i+1}$ *for* i = 1, . . . , $I-1$. *In addition, assume that* $w_{11} > w_{22}$ *and there is intermediate dominance, i.e.,*

$$w_{ii} \geq w_{ij} \geq w_{jj} \tag{7.10}$$

for every i *and every* $j > i$. *Then allele* $\mathcal{A}_1$ *is fixed as* $t \to \infty$. *The corresponding equilibrium is globally asymptotically stable.*

Proof. The assumptions imply $w_{1i} \geq w_{ii} \geq w_{Ii}$ for every $i \in$ I and $w_{11} > w_{I1}$ or $w_{I1} > w_{II}$. It follows that $w_1 = \sum_i w_{1i}p_i \geq \sum_i w_{Ii}p_i = w_I$ and, if $p_1 \neq 0$ and $p_I \neq 0$,

$$w_1 > w_I\,. \tag{7.11}$$

Therefore, we obtain

$$\left(\frac{p_I}{p_1}\right)' = \frac{p_I'}{p_1'} = \frac{p_I w_I}{p_1 w_1} < \frac{p_I}{p_1} \tag{7.12}$$

if $p_1 > 0$ and $p_I > 0$. Hence, $p_I(t) \to 0$ as $t \to \infty$ provided $p_I < 1$ and $p_1 > 0$. Now we can repeat this argument with p_1 and p_{I-1}. Proceeding inductively, we obtain $p_1(t) \to 1$ as $t \to \infty$. □

Theorem 7.7. *Suppose that migration is sufficiently weak and there is partial dominance in every deme, i.e.,*

$$w_{ii,\alpha} > w_{ij,\alpha} > w_{jj,\alpha} \quad or \quad w_{ii,\alpha} < w_{ij,\alpha} < w_{jj,\alpha} \tag{7.13}$$

for every i, *every* $j \neq i$, *and every* α.

(a) Generically, there is global convergence to an asymptotically stable equilibrium at which at most alleles are present. Thus, the number of demes is a generic upper bound for the number of alleles that can be maintained at a stable equilibrium.

(b) If $\leq I$, *then there is an open set of parameters such that alleles are segregating at a globally asymptotically stable equilibrium.*

Proof. Corollary 7.6 shows that, in the absence of migration, one allele is xed in every deme. The parameter combinations satisfying the assumptions of the theorem clearly form an open set of all possible parameter combinations. Therefore, without migration, at most alleles can be maintained at an asymptotically stable equilibrium, and this can be achieved on an open set in the parameters space. Moreover, this equilibrium is globally asymptotically stable. Therefore, Theorem 7.3 yields statement (a) for weak migration. Clearly, the same set of alleles as without migration occurs at this equilibrium.

If $\leq I$, we still obtain an open set of parameters if we choose tnesses such that in each deme a di erent allele has the highest homozygous tness. Hence, the upper bound can be achieved on an open set, and Theorem 7.3 yields statement (b). □

8 Strong migration

If migration is much stronger than selection, we expect that rapid convergence to spatial quasi-homogeneity occurs. After this short initial phase, evolution should be approximately panmictic with suitably averaged allele frequencies. Because in the absence of selection, there exists a globally attracting manifold of equilibria, so that the dynamics is not gradient like, the derivation of perturbation results is much more delicate than for weak migration. Since the fundamental ideas in the proofs of the most relevant results are essentially the same as if selection acts on many loci, we defer the analysis of strong migration to Sect. 10.4, where the two-locus case is treated.

9 Miscellaneous one-locus results

Here, a number of further interesting results and examples are collected, mostly without proof.

9.1 General migration

We admit a general (constant) backward migration matrix.

9.1.1 No dominance

The following generalizes Theorem 5.8 for the Levene model.

Theorem 9.1 (Nagylaki and Lou 2001). *Without dominance, the number of demes is a generic upper bound on the number of alleles that can be maintained at any equilibrium.*

This theorem also holds for hard selection. An example showing that the upper bound can be achieved if $I =$ is obtained by setting $v_{i,\alpha} = u_i\delta_{i\alpha}$, where $u_i > 0$. The internal equilibrium can be written as $\hat{p} = \frac{1}{2}(I - \frac{1}{2}M)^{-1}M$, and convergence is geometric (at a rate $\leq \frac{1}{2}$).

9.1.2 Two alleles and submultiplicative fitnesses

We assume two alleles and present a number of results for submultiplicative tnesses. Throughout, $\xi \in \mathsf{S}_\Gamma$ is the left principal eigenvector of M; cf. (10.24).

Theorem 9.2 (Karlin and Campbell 1980, Result I). *If* ≥ 2 *and fitnesses are submultiplicative in both demes, then at most one monomorphic equilibrium can be asymptotically stable and have a geometric rate of convergence.*

The proof relies on the following very useful result:
Lemma 9.3 (Friedland and Karlin 1975). *If M is a stochastic $n \times n$ matrix and D is a diagonal matrix with entries $d_i > 0$ along the diagonal, then*

$$\rho(MD) \geq \prod_{i=1}^{n} d_i^{\xi_i} \tag{9.1}$$

holds, where $\rho(MD)$ is the spectral radius of MD.

Without restrictions on the migration matrix, the su cient condition

$$\prod_{\alpha} (1/y_\alpha)^{\xi_\alpha} > 1 \tag{9.2}$$

for protection of A_1 is sharp. This can be veri ed for a circulant stepping stone model, when $\xi_\alpha = 1/$.

The conclusion of Theorem 9.2 remains valid under some other conditions (see Karlin and Campbell 1980). For instance, if migration is doubly stochastic, then $\xi_\alpha = 1/$ for every α and $\rho(MD) \geq \prod_\alpha d_\alpha^{1/\Gamma}$. Therefore, the compound condition

$$\prod_{\alpha} x_\alpha y_\alpha < 1 \tag{9.3}$$

implies the conclusion of the theorem.

Here is another interesting result:

Theorem 9.4 (Karlin and Campbell 1980, Result III). *If* $= 2$ *and fitnesses are multiplicative, then there exists a unique asymptotically stable equilibrium.*

Because the proof given by Karlin and Campbell (1980) is erroneous, we present a correct proof (utilizing their main idea). In addition, global stability was claimed without proof. However, it is not obvious how to exclude existence of, for instance, limit cycles.

Proof of Theorem 9.4. We recall that a diploid discrete-time model with multiplicative fitnesses is equivalent to a haploid model, in which fitnesses are assigned to alleles (Section 2.2). Therefore, we treat the haploid model and assume without loss of generality that the fitnesses of alleles $\mathcal{A}_1$ and $\mathcal{A}_2$ are $s_1 > 0$ and 1 in deme 1, and $s_2 > 0$ and 1 in deme 2. Let the frequency of $\mathcal{A}_1$ in demes 1 and 2 be p_1 and p_2, respectively. Then the equilibrium condition is the following:

$$(1-m_1)\frac{s_1p_1}{s_1p_1+1-p_1} + m_1\frac{s_2p_2}{s_2p_2+1-p_2} = p_1\,, \tag{9.4a}$$

$$m_2\frac{s_1p_1}{s_1p_1+1-p_1} + (1-m_2)\frac{s_2p_2}{s_2p_2+1-p_2} = p_2\,. \tag{9.4b}$$

We solve the first equation for p_2 and obtain

$$p_2 = \frac{p_1[(1-p_1)(1-s_1)+s_1m_1]}{p_1(1-p_1)(1-s_1)(1-s_2)+m_1(s_2+s_1p_1-s_2p_1)}\,. \tag{9.5}$$

Substituting this into the second and multiplying with the nominator, we find that every equilibrium must satisfy

$$p_1(1-p_1)(1-p_1+s_1p_1)A(p_1) = 0\,, \tag{9.6}$$

where

$$\begin{aligned} A(p_1) = {} & m_1[(1-s_1)(1-s_2+m_2s_2)+m_1s_1(1-s_2)] \\ & -(1-s_1)\left\{(1-m_2)(1-s_1)(1-s_2)+m_1[1-s_2(1-m_2)+s_1(1-m_2-s_2)]\right\}p_1 \\ & +(1-m_2)(1-s_1)^2(1-s_2)p_1^2\,. \end{aligned} \tag{9.7a}$$

We want to show that $A(p_1)$ always has two zeros because then zeros in $(0,1)$ can emerge only by bifurcating through either $p_1 = 0$ or $p_1 = 1$. Therefore, we calculate the discriminant:

$$\begin{aligned} D = {} & (1-m_2)^2\sigma^2\tau^2 + 2m_1(1-m_2)\sigma\tau[m_2(2+\sigma-\tau)-\sigma\tau] \\ & +m_1^2[m_2^2(\sigma+\tau)^2 - 2m_2\sigma(2+\sigma-\tau)\tau+\sigma^2\tau^2]\,, \end{aligned} \tag{9.8a}$$

where we set $s_1 = 1+\sigma$ and $s_2 = 1-\tau$ with $\sigma > 0$ and $0 < \tau < 1$.

Now we consider D as a (quadratic!) function in m_1. To show that $D(m_1) > 0$ if $0 < m_1 < 1$, we compute

$$D(0) = (1-m_2)^2\sigma^2\tau^2 > 0\,,\ D(1) = m_2^2[\tau-\sigma(1-\tau)]^2 > 0\,, \tag{9.9}$$

and

$$D'(0) = 2(1-m_2)\sigma\tau[m_2(2+\sigma-\tau)-\sigma\tau]\,. \tag{9.10}$$

We distinguish two cases.

1. If $m_2(2+\sigma-\tau) > \sigma\tau$, then $D'(0) > 0$ and there can be no zero in $(0,1)$. (If D is concave, then $D(p_1) > 0$ on $[0,1]$ because $D(1) > 0$; if D is convex, then $D'(p_1) > 0$ holds for every $p_1 > 0$.)

2. If $m_2(2+\sigma-\tau) < \sigma\tau$, hence $m_2 < \frac{\sigma\tau}{2+\sigma-\tau}$, we obtain

$$\begin{aligned} D'(1) &= 2m_2[-\sigma\tau(2+\sigma-\tau-\sigma\tau) + m_2(\sigma^2(1-\tau)+\tau^2+\sigma\tau^2)] \\ &< -2m_2\frac{4\sigma(1+\sigma)(1-\tau)\tau}{2+\sigma-\tau}\,, \end{aligned} \tag{9.11a}$$

whence $D'(1) < 0$. Therefore, D has no zero in $(0,1)$. Thus, we have shown that $A(p_1) = 0$ has always two real solutions.

For the rest of the proof we can follow Karlin and Campbell: If $s_1 = 1$ and $s_2 < 1$, there are no polymorphic equilibria, $p_1 = 0$ is stable and $p_1 = 1$ is unstable. As s_1 increases, a bifurcation event at $p_1 = 0$ occurs before $p_1 = 1$ becomes stable. At this bifurcation event, $p_1 = 0$ becomes unstable and a stable polymorphic equilibrium bifurcates off $p_1 = 0$. Because the constant term $m_1[(1-s_1)(1-s_2+m_2s_2)+m_1s_1(1-s_2)]$ in $A(p_1)$ is linear in s_1, no further polymorphic equilibria can appear as s_1 increases until $p = 1$ becomes stable, which then remains stable for larger s_1. □

Karlin and Campbell (1980) showed that for some migration patterns, Theorem 9.4 remains true for an arbitrary number of demes. The Levene model is one such example. In fact, Theorem 5.15 is a much stronger result. It is an open problem whether Theorem 9.4 holds for arbitrary migration patterns if there are more than two demes. An interesting, related result is the following.

Theorem 9.5 (Karlin and Campbell 1980, Result IV). *Let* ≥ 2 *and let* M *be arbitrary but fixed. If there exists a unique, globally attracting equilibrium under multiplicative fitnesses, then there exists a unique, globally attracting equilibrium for arbitrary submultiplicative fitnesses.*

9.1.3 Uniform selection

Throughout this section, we assume uniform selection, i.e.,

$$w_{ij,\alpha} = w_{ij} \quad \text{for every } i,\ j, \text{ and every } \alpha. \tag{9.12}$$

We have seen that strong migration leads to a panmictic limit. Under spatially uniform selection, one might also expect that population structure leaves no genetic traces. However, this is not always true as shown by our Example **??** with underdominance and weak migration. Indeed, if we have two diallelic demes with the same underdominant selection in both, then under weak migration there are nine equilibria, four of which are asymptotically stable. These are the two monomorphic equilibria and the two equilibria where each of the alleles is close to fixation in one deme and rare in the other. Only three of the equilibria are uniform, i.e., have the same allele frequencies in both demes. These are the two monomorphic equilibria and the 'central' equilibrium.

In the following we state sufficient conditions under which there is no genetic indication of population structure. We call $\hat{p} \in \mathsf{S}_I^\Gamma$ a uniform selection equilibrium if every $\hat{p}_{\cdot,\alpha}$ is an equilibrium of the pure selection dynamics (7.3) and $\hat{p}_{\cdot,\alpha} = \hat{p}_{\cdot,\beta}$ for every α, β.

Theorem 9.6 (Nagylaki and Lou 2007, Theorem 5.1)**.** *If $\hat{p} \in \mathsf{S}_I^\Gamma$ is a uniform selection equilibrium, then $\hat{p}$ is an equilibrium of the (full) migration-selection dynamics* (3.5)*, and $\hat{p}$ is either asymptotically stable for both* (7.3) *and* (3.5)*, or unstable for both systems.*

It can also be shown that the ultimate rate of convergence to equilibrium is determined entirely by selection and is independent of migration.

Next, one may ask for the conditions when the solutions of (3.5) converge globally to a uniform selection equilibrium. One may expect global convergence under migration if the uniform selection equilibrium is globally asymptotically stable without migration. So far, only weaker results could be proved.

Theorem 9.7 (Nagylaki and Lou 2007, Sections 5.2 and 5.3)**.** *Suppose there is a uniform selection equilibrium that is globally asymptotically stable in the absence of migration. Each of the following conditions implies global convergence of solutions to $\hat{p}$ under migration and selection.*

1. Migration is weak and, without migration, every equilibrium is hyperbolic.

2. Migration is strong, M is ergodic, and every equilibrium of the strong-migration limit is hyperbolic.

3. The continuous-time model (6.10) *applies, $\mu_{\alpha\beta} > 0$ for every pair α, β with $\alpha \neq \beta$, and $\hat{p}$ is internal in the absence of migration (hence, also with migration).*

4. The continuous-time model (6.10) *applies, $\mu_{\alpha\beta} = \mu_{\beta\alpha}$ for every pair α, β, and $\hat{p}$ is internal.*

9.2 Special migration patterns

Here, additional special migration patterns are introduced that play an important role in population genetics and ecology. For detailed results on the stepping-stone and many other models, see Karlin (1982).

9.2.1 The linear stepping-stone model

In this model the demes are arranged in a linear order and individuals can reach only one of the neighboring demes. In generalization of (3.21), one may assume that the backward migration matrix is of a general tridiagonal form:

$$M = \begin{pmatrix} n_1 & r_1 & 0 & \dots & 0 \\ q_2 & n_2 & r_2 & & 0 \\ \vdots & & \ddots & & \vdots \\ 0 & & q_{\Gamma-1} & n_{\Gamma-1} & r_{\Gamma-1} \\ 0 & \dots & 0 & q_\Gamma & n_\Gamma \end{pmatrix}, \tag{9.13}$$

where $n_\alpha \geq 0$ and $q_\alpha + n_\alpha + r_\alpha = 1$ for every α, and $q_\alpha > 0$ for $\alpha \geq 1$ and $r_\alpha > 0$ for $\alpha \leq \Gamma - 1$. This matrix admits variation of the migration flow between neighboring demes. Sometimes, also circular or infinite variants have been studied.

The following simple, explicit criterion for protection of $\mathcal{A}_1$ was derived by Karlin (1982):

$$\sum_\alpha \frac{\pi_\alpha}{y_\alpha} \Big/ \sum_\alpha \pi_\alpha \; > 1 \,. \tag{9.14}$$

Here, tnesses are given by (4.1), and

$$\pi_\alpha = \frac{r_{\alpha-1} r_{\alpha-2} \cdots r_1}{q_\alpha q_{\alpha-1} \cdots q_2} \tag{9.15}$$

if $\alpha \geq 2$, and $\pi_1 = 1$. This is a simple consequence of Lemma 9.3. For the homogeneous stepping-stone model with equal demes sizes, i.e., M given by (3.21), (9.14) simpli es to

$$\frac{1}{-} \sum_\alpha \frac{1}{y_\alpha} > 1 \,, \tag{9.16}$$

which is the same as condition (4.34) in the Levene model with equal deme sizes.

9.2.2 The island model

We consider a population living on an island. Each generation, a proportion a of adults is removed by mortality or emigration and a fraction b of migrants with constant allele frequencies $\hat{q}_i$ is added. A simple interpretation is that of one-way migration from a continent, with a big equilibrium population with allele frequencies $\hat{q}_i > 0$, to an island. Sometimes, $\hat{q}_i$ is interpreted as the average frequency over (in nitely) many islands.

Assuming random mating on the island, the dynamics of allele frequencies p_i on the island becomes

$$p_i' = (1-m) p_i \frac{w_i}{w} + m\hat{q}_i \,, \tag{9.17}$$

where w_i is the tness of allele $\mathcal{A}_i$ on the island and $m = b/(1 - a + b)$. Thus, m is the fraction of zygotes with immigrant parents. Throughout we assume $0 < m < 1$.

If we de ne $u_{ij} = m\hat{q}_j$ and consider u_{ij} as the mutation rate from $\mathcal{A}_i$ to $\mathcal{A}_j$, a special case of the (multiallelic) mutation-selection model is obtained (the so-called house-of-cards model). Therefore (Burger 2000, pp. 102-103), (9.17) has the Lyapunov function

$$V(p) = w(p)^{1-m} \prod_i p_i^{2m\hat{q}_i} \,. \tag{9.18}$$

It follows that all trajectories are attracted by the set of equilibria.

An interesting problem is to determine the conditions under which an `island allele' persist in the population despite immigration of other alleles from the continent. Clearly, no allele carried to the island recurrently by immigrants can be lost.

We investigate the diallelic case and consider the alleles $\mathcal{A}_1$ and $\mathcal{A}_2$, with frequencies p and $1-p$, and $q_1 = 0$. Thus, all immigrants are $\mathcal{A}_2\mathcal{A}_2$. For the fitnesses on the island, we assume

$$w_{11} = 1 + s\,,\ w_{12} = 1 + hs\,,\ w_{22} = 1 - s\,, \tag{9.19}$$

where $0 < s \leq 1$ and $-1 \leq h \leq 1$. Therefore, $\mathcal{A}_1$ evolves according to

$$p' = f(p) = (1-m)p\frac{w_1}{w}\,. \tag{9.20}$$

We outline the analysis of (9.20). Since $f(1) = 1 - m < 1$, this confirms that $\mathcal{A}_2$ cannot be lost ($p = 1$ is not an equilibrium). Because

$$f(p) = p(1-m)\frac{w_{12}}{w_{22}} + O(p^2) \tag{9.21}$$

as $p \to 0$, the allele $\mathcal{A}_1$ is protected if

$$m < 1 - \frac{w_{22}}{w_{12}}\,. \tag{9.22}$$

Obviously, $p = 0$ is an equilibrium. If there is no other equilibrium, then it must be globally asymptotically stable (as is also obvious from $f(1) < 1$, which implies $p' < p$).

The equilibria with $p \neq 0$ satisfy

$$\bar{w} = (1-m)w_1\,, \tag{9.23}$$

which is quadratic in p. With the fitnesses (9.19), the solutions are

$$\hat{p}_\pm = \frac{1}{4h}\left[1 + 3h + m(1-h) \pm \sqrt{(1-h)^2(1+m)^2 + 8hm(1+1/s)}\right]\,, \tag{9.24}$$

These solutions give rise to feasible equilibria if $0 \leq p_\pm \leq 1$. As $h \to 0$, (9.24) gives the correct limit,

$$\hat{p}_- = \frac{1 - m/s}{1+m} \quad \text{if } h = 0. \tag{9.25}$$

We define

$$h_0 = -\frac{1+m}{3-m}\,, \tag{9.26a}$$

$$\mu_1 = 1 + h(1-m)\,, \tag{9.26b}$$

$$\mu_2 = -m - \frac{(1-h)^2(1+m)^2}{8h}\,. \tag{9.26c}$$

Then $\mu_2 > \mu_1$ if and only if $h < h_0$. If $\mu_2 < \mu_1$, then only $\hat{p}_+$ is not admissible. As m increases from 0 to 1, h_0 decreases from $-\frac{1}{3}$ to -1. Hence, if there is no dominance or the fitter allele $\mathcal{A}_1$ is (partially) dominant ($0 \leq h \leq 1$), then $h > h_0$. If $\mathcal{A}_1$ is recessive, then $h < h_0$. For fixed h and s it is straightforward, but tedious, to study the dependence of $\hat{p}_+$ and $\hat{p}_-$ on m.

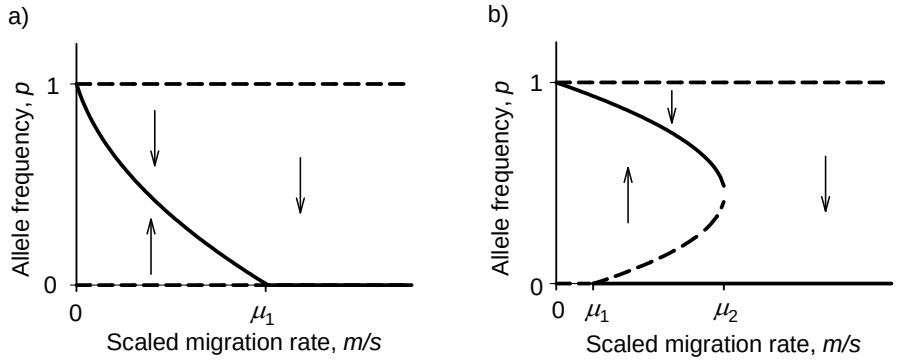

Figure 9.1: Bifurcation patterns for the one-locus continent-island model. Bold lines indicate an asymptotically stable equilibrium, dashed lines an unstable equilibrium. Figure a displays the case $h_0 \leq h \leq 1$, and Figure b the case $-1 \leq h < h_0$. The parameters are $s = 0.1$, and $h = 0.5$ and $h = -0.9$ in cases a and b, respectively. In a, we have $\mu_1 \approx 1.41$; in b, $\mu_1 \approx 0.11$, $\mu_2 \approx 0.5$

The results of this analysis can be summarized as follows (for an illustration, see Figure 9.1):

Theorem 9.8. *1. Let $m/s < \mu_1$. Then 0 and p_- are the only equilibria and $p(t) \to \hat{p}_-$ as $t \to \infty$. Thus, for sufficiently weak migration, a unique polymorphism is established independently of the degree of dominance and the initial condition.*

2. Let $m/s > \mu_2$ and $-1 \leq h < h_0$, or $m/s \geq \mu_1$ and $h_0 \leq h \leq 1$, i.e., migration is strong relative to selection. Then there exists no internal equilibrium and $p(t) \to 0$ as $t \to 0$, i.e., the continental allele $\mathcal{A}_2$ becomes fixed.

3. Let $\mu_1 < m/s \leq \mu_2$ and $-1 \leq h < h_0$, i.e., migration is moderately strong relative to selection and the fitter allele is (almost) recessive. Then there are the three equilibria 0, $\hat{p}_+$, and $\hat{p}_-$, where $0 < \hat{p}_+ < \hat{p}_-$, and

$$p(t) \to 0 \quad \text{if } p(0) < \hat{p}_+ , \tag{9.27a}$$

$$p(t) \to \hat{p}_- \quad \text{if } p(0) > \hat{p}_+ . \tag{9.27b}$$

For a detailed proof, see Nagylaki (1992, Chapter 6.1). The global dynamics of the diallelic continent-island model admitting evolution on the continent is derived in Nagylaki (2009a). Sometimes immigration from two continents is considered (Christiansen 1999). Some authors call our general migration model with n demes the n-island model (e.g., Christiansen 1999).

The following (symmetric) island model is a standard model in investigations of the

consequences of random drift and mutation in nite populations:

$$m_{\alpha\alpha} = 1 - m\,, \tag{9.28a}$$

$$m_{\alpha\beta} = \frac{m}{-1} \text{ if } \alpha \neq \beta\,. \tag{9.28b}$$

Clearly, migration is doubly stochastic in this model and there is no isolation by distance. In the special case when all deme sizes are equal, i.e., $c_\alpha = 1/$, (9.28) reduces to a special case of the Deakin model, (3.17), with $m = \mu(1 - {}^{-1})$. In this, and only this case, the island model is conservative and the stationary distribution of M is $c = e/$.

9.3 Some open problems

In passing, we have mentioned several open problems. However, there are many more. For instance, what can happen if migration is neither weak nor strong? Where is the transition from the case of weak to that of strong migration? (Answers will depend on the particular migration pattern and selection scheme; migration patterns with a single parameter measuring the strength of migration will be most conducive.) When is it the case that lower migration favors more polymorphism? (It is the case for two demes or the Deakin model.) For which important quantities (e.g., equilibria, measures of diversity, mean tness) can rst-order approximations be derived if migration is either weak or strong? Can error estimates for such rst-order approximations be derived? Some scenarios have been found in which qualitatively new dynamics and equilibrium structures occur if migration is neither weak nor strong.

10 Multilocus models

Because many phenotypic traits are determined by many gene loci, selection acts on many loci. If loci are on the same chromosome, especially if they are within a short physical distance, they can not be treated independently. In order to understand the evolutionary e ects of selection on multiple loci, models have to be developed and studied that take linkage and recombination into account. Before outlining some of the results that can be obtained for multilocus models of selection and migration, we introduce the basic models describing the interaction of selection and recombination and point out some of their fundamental properties. For simplicity, we con ne attention to two loci, mostly with two alleles. All models and results treated below can be extended to multiple loci, each with an arbitrary number of alleles (Bürger 2009a,b, Nagylaki 2009b). This, however, requires substantial additional technical e ort.

To illustrate the e ects of recombination, we start with the simplest possible situation.

10.1 Recombination between two loci

We consider two loci, $\mathcal{A}$ and $\mathcal{B}$, each with two alleles, $\mathcal{A}_1$, $\mathcal{A}_2$, and $\mathcal{B}_1$, $\mathcal{B}_2$. Therefore, there are four possible gametes, $\mathcal{A}_1\mathcal{B}_1$, $\mathcal{A}_1\mathcal{B}_2$, $\mathcal{A}_2\mathcal{B}_1$, $\mathcal{A}_2\mathcal{B}_2$, and 16 diploid genotypes. If, as usual, $\mathcal{A}_i\mathcal{B}_j/\mathcal{A}_k\mathcal{B}_\ell$ and $\mathcal{A}_k\mathcal{B}_\ell/\mathcal{A}_i\mathcal{B}_j$ are indistinguishable, then only 10 di erent unordered genotypes remain. In addition, we assume that there is no position e ect, i.e., the double heterozygotes $\mathcal{A}_1\mathcal{B}_1/\mathcal{A}_2\mathcal{B}_2$ and $\mathcal{A}_1\mathcal{B}_2/\mathcal{A}_2\mathcal{B}_1$ are indistinguishable. Therefore, it is su cient the consider the nine two-locus genotpyes obtained by all combinations of $\mathcal{A}_i\mathcal{A}_j$ and $\mathcal{B}_k\mathcal{B}_\ell$ ($i, j, k, \ell \in \{1, 2\}$).

Genes on di erent chromosomes are separated during meiosis with probability one half (Mendel's Principle of Independent Assortment). If the loci are on the same chromosome, they may become separated by a recombination event (a crossover) between them. We denote this *recombination probability* by r. The value of r usually depends on the distance between the two loci along the chromosome. Loci with $r = 0$ are called completely linked (and may be treated as a single locus), and loci with $r = \frac{1}{2}$ are called unlinked. The maximum value of $r = \frac{1}{2}$ occurs for loci on di erent chromosomes, because then all four gametes are produced with equal frequency $\frac{1}{4}$. Thus, the recombination rate satis es $0 \le r \le \frac{1}{2}$.

If, for instance, in the initial generation only the genotypes $\mathcal{A}_1\mathcal{B}_1/\mathcal{A}_1\mathcal{B}_1$ and $\mathcal{A}_2\mathcal{B}_2/\mathcal{A}_2\mathcal{B}_2$ are present, then in the next generation only these double homozygotes, as well as the two double heterozygotes $\mathcal{A}_1\mathcal{B}_1/\mathcal{A}_2\mathcal{B}_2$ and $\mathcal{A}_1\mathcal{B}_2/\mathcal{A}_2\mathcal{B}_1$ will be present. After further generations of random mating, all other genotypes will occur, but not immediately at their equilibrium frequencies. The formation of gametic types other than $\mathcal{A}_1\mathcal{B}_1$ or $\mathcal{A}_2\mathcal{B}_2$ requires that recombination between the two loci occurs.

We denote the frequency of the gamete $\mathcal{A}_i\mathcal{B}_j$ by p_{ij} and, at rst, admit an arbitrary number of alleles at each locus. Let the frequencies of the alleles $\mathcal{A}_i$ at the rst ($\mathcal{A}$) locus be denoted by $p_i^{(1)}$ and those of the alleles $\mathcal{B}_j$ at the second ($\mathcal{B}$) locus by $p_j^{(2)}$. They are given by

$$p_i^{(1)} = \sum_j p_{ij} \text{ and } p_j^{(2)} = \sum_i p_{ij} \,. \tag{10.1}$$

The allele frequencies are no longer su cient to describe the genetic composition of the population because, in general, they do not evolve independently. *Linkage equilibrium*

(LE) is de ned as the state in which

$$p_{ij} = p_i^{(1)} p_j^{(2)} \tag{10.2}$$

holds for every i and j. Otherwise the population is said to be in $linkage\ disequilibrium$ (LD). LD is equivalent to statistical dependence of allele frequencies between loci.

Given p_{ij}, we want to nd the gametic frequencies p'_{ij} in the next generation after random mating. The derivation of the recursion equation is based on the following basic fact of Mendelian genetics: an individual with genotype $\mathcal{A}_i\mathcal{B}_j/\mathcal{A}_k\mathcal{B}_l$ produces gametes of parental type if no recombination occurs (with probability $1 - r$), and recombinant gametes if recombination between the two loci occurs (with probability r). Therefore, the fraction of gametes $\mathcal{A}_i\mathcal{B}_j$ and $\mathcal{A}_k\mathcal{B}_l$ is $\frac{1}{2}(1 - r)$ each, and that of $\mathcal{A}_i\mathcal{B}_l$ and $\mathcal{A}_k\mathcal{B}_j$ is $\frac{1}{2}r$ each. From these considerations, we see that the frequency of gametes of type $\mathcal{A}_i\mathcal{B}_j$ in generation $t + 1$ produced without recombination is $(1 - r)p_{ij}$, and that produced with recombination is $rp_i^{(1)}p_j^{(2)}$ because of random mating. Thus,

$$p'_{ij} = (1 - r)p_{ij} + rp_i^{(1)}p_j^{(2)} . \tag{10.3}$$

This shows that the allele frequencies are conserved, but the gamete frequencies are not, unless the population is in LE, (10.2). Commonly, LD between alleles $\mathcal{A}_i$ and B_j is measured by the parameter

$$D_{ij} = p_{ij} - p_i^{(1)}p_j^{(2)} . \tag{10.4}$$

The D_{ij} are often called linkage disequilibria. From (10.3) and (10.4) we infer

$$D'_{ij} = (1 - r)D_{ij} \tag{10.5}$$

and

$$D_{ij}(t) = (1 - r)^t D_{ij}(0) . \tag{10.6}$$

Therefore, unless $r = 0$, linkage disequilibria decay at the geometric rate $1 - r$ and LE is approached gradually without oscillation.

From now on we assume two alleles per locus. A simple calculation reveals that

$$D = p_{11}p_{22} - p_{12}p_{21} \tag{10.7}$$

satis es

$$D = D_{11} = -D_{12} = -D_{21} = D_{22} . \tag{10.8}$$

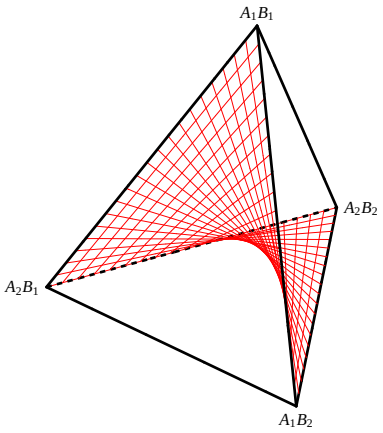

Figure 10.1: The tetrahedron represents the state space S_4 of the two-locus two-allele model. The vertices correspond to fixation of the labeled gamete, and frequencies are measured by the (orthogonal) distance from the opposite boundary face. At the center of the simplex all gametes have frequency $\frac{1}{4}$. The two-dimensional (red) surface is the LE manifold, $D = 0$. The states of maximum LD, $D = \pm\frac{1}{4}$, are the centers of the edges connecting $\mathcal{A}_1\mathcal{B}_2$ to $\mathcal{A}_2\mathcal{B}_1$ and $\mathcal{A}_1\mathcal{B}_1$ to $\mathcal{A}_2\mathcal{B}_2$.

Thus, the recurrence equations for the gamete frequencies, (10.3), may be rewritten as

$$p'_{ij} = p_{ij} + (-1)^{i+j} r D\,, \quad i,j \in \{1,2\}\,. \tag{10.9}$$

The two-locus gametic frequencies are the elements of the simplex S_4 and may be represented geometrically by the points in a tetrahedron. The subset where $D = 0$ forms a two-dimensional manifold and is called the *linkage-equilibrium manifold*, or the *Wright manifold*. It is displayed in Figure 10.1.

If $r > 0$, (10.6) implies that all solutions of (10.9) converge to the LE manifold along straight lines, because the allele frequencies $p_1^{(1)} = p_{11} + p_{12}$ and $p_1^{(2)} = p_{11} + p_{21}$ remain constant, and sets of the form $p_{11} + p_{12} = \text{const.}$ represent planes in this geometric picture. The LE manifold is invariant under the dynamics (10.9).

10.2 Two diallelic loci under selection

To introduce selection, we assume that viability selection acts on juveniles. Then recombination and random mating occurs. Since selection acts on diploid individuals, we assign fitnesses to two-locus genotypes. We denote the fitness of genotype $\mathcal{A}_i\mathcal{B}_j/\mathcal{A}_k\mathcal{B}_\ell$ ($i,j,k,\ell \in \{1,2\}$) by $w_{ij,k\ell}$. We always assume $w_{ij,k\ell} = w_{k\ell,ij}$ because, usually, the corresponding genotypes are indistinguishable. Then the marginal fitness of gamete ij is

de ned as

$$w_{ij} = \sum_{k,\ell} w_{ij,k\ell} p_{k\ell} \,, \tag{10.10}$$

and the mean tness of the population is

$$w = \sum_{i,j} w_{ij} p_{ij} = \sum_{i,j,k,\ell} w_{ij,k\ell} p_{ij} p_{k\ell} \,. \tag{10.11}$$

If we assume, as is frequently the case, that there is no position e ect, i.e., $w_{11,22} = w_{12,21}$, then simple calculations yield the following selection-recombination dynamics:

$$p'_{ij} = p_{ij} \frac{w_{ij}}{w} + (-1)^{i+j} \frac{w_{11,22}}{w} rD \,, \quad i,j \in \{1,2\} \,. \tag{10.12}$$

This is a much more complicated dynamical system than either the pure selection dynamics (2.6) or the pure recombination dynamics (10.9), and has been studied extensively (for a review, see Bürger 2000, Sects. II.2 and VI.2). In general, mean tness may decrease and is no longer maximized at an equilibrium.

In addition, the existence of stable limit cycles has been established for this discrete-time model (Hastings 1981b, Hofbauer and Iooss 1984) as well as for the corresponding continuous-time model (Akin 1979, 1982). Essentially, the demonstration of limit cycles requires that selection coe cients and recombination rates are of similar magnitude.

There is a particularly important special case in which the dynamics is simple. This is the case of *no epistasis*, or *additive fitnesses*. Then there are constants $u_{ij}^{(n)}$ such that

$$w_{ij,k\ell} = u_{ik}^{(1)} + u_{j\ell}^{(2)} \quad \text{for every } i,j,k,\ell \in \{1,2\} \,. \tag{10.13}$$

In the absence of epistasis, i.e., if (10.13) holds, mean tness w is a (strict) Lyapunov function (Ewens 1969). In addition, a point p is an equilibrium point of (10.12) if and only if it is both a selection equilibrium for each locus and it is in linkage equilibrium (Lyubich 1992, Nagylaki et al. 1999). In particular, the equilibria are the critical points of mean tness.

The reason for this increased complexity of two-locus (or multlocus) systems lies not so much in the increased dimensionality but arises mainly from the fact that epistatic selection generates nonrandom associations (LD) among the alleles at di erent loci. Recombination breaks up these associations to a certain extent but changes gamete frequencies in a complex way. Thus, there are di erent kinds of interacting nonlinearities arising in the dynamical equations under selection and recombination.

10.3 Selection, recombination, and migration

We extend the migration-selection model of Section 3 by assuming that selection acts on two recombining loci, each with two alleles, as described above. This is su cient to provide an accurate impression of what kind of results have been achieved. Because of the complexity of the general model, useful analytical results can be obtained essentially only for limiting cases or for very special cases. Whereas the former can be sometimes extended using perturbation theory to obtain some general insights, the latter are mainly useful to study speci c biological questions or to demonstrate the kind of complexity that can arise. We will rst deal with a number of important and interesting limiting cases.

10.3.1 The dynamical equations

Because we assume random mating within each deme, the population can be described by the gamete frequencies (among zygotes) in each of the demes. We employ a straightforward extension of the above terminology. The frequency of gamete ij in deme α is now denoted by $p_{ij,\alpha}$, and the allele frequencies at the rst and second locus are

$$p^{(1)}_{i,\alpha} = \sum_j p_{ij,\alpha} \quad \text{and} \quad p^{(2)}_{i,\alpha} = \sum_j p_{ji,\alpha}\,, \tag{10.14}$$

respectively ($i, j \in \{1, 2\}$). We write

$$D_\alpha = p_{11,\alpha}p_{22,\alpha} - p_{12,\alpha}p_{21,\alpha} \tag{10.15}$$

for the measure of LD in deme .

We shall use the following column vectors:

$$p_{ij} = (p_{ij,1}, \ldots, p_{ij,\Gamma})^\top \in \mathbb{R}^\Gamma\,, \tag{10.16a}$$

$$p_{\cdot,\alpha} = (p_{11,\alpha}, p_{12,\alpha}, p_{21,\alpha}, p_{22,\alpha})^\top \in S_4\,, \tag{10.16b}$$

$$p = \left(p^\top_{\cdot,1}, \ldots, p^\top_{\cdot,\Gamma}\right)^\top \in S_4^\Gamma\,, \tag{10.16c}$$

$$p^{(n)}_i = \left(p^{(n)}_{i,1}, \ldots, p^{(n)}_{i,\Gamma}\right)^\top \in \mathbb{R}^\Gamma\,, \tag{10.16d}$$

$$D = (D_1, \ldots, D_\Gamma)^\top \in \mathbb{R}^\Gamma\,. \tag{10.16e}$$

We assign the tness $w_{ij,k\ell;\alpha}$ to the genotype $ij, k\ell$ in deme α. Then the marginal tness of gamete ij in deme α and the mean tness of the population in deme α are

$$w_{ij,\alpha} = w_{ij,\alpha}(p_{\cdot,\alpha}) = \sum_{k,\ell} w_{ij,k\ell;\alpha}p_{k\ell,\alpha} \tag{10.17a}$$

and

$$w_\alpha = w_\alpha(p_{\cdot,\alpha}) = \sum_{i,j,k,\ell} w_{ij,k\ell;\alpha} p_{ij,\alpha} p_{k\ell,\alpha}\,, \tag{10.17b}$$

respectively.

The life cycle starts with zygotes in Hardy-Weinberg proportions. Selection acts in each deme on the newly born o spring. Then recombination occurs followed by adult migration and random mating within in each deme. This life cycle extends the one in Sect. 3.2 and we can combine equations (3.5a) and (10.12) to obtain the di erence equations describing evolution under selection, recombination, and migration:

$$p'_{ij,\alpha} = \sum_\beta m_{\alpha\beta} p^{\#}_{ij,\beta}\,, \tag{10.18a}$$

where

$$p^{\#}_{ij,\alpha} = p_{ij,\alpha}\frac{w_{ij,\alpha}}{w_\alpha} + (-1)^{i+j}\frac{w_{11,22;\alpha}}{w_\alpha} r D_\alpha\,. \tag{10.18b}$$

We view (10.18) as a dynamical system on S_4^Γ. We leave it to the reader to check the obvious fact that the processes of migration and recombination commute.

With multiple multiallelic loci, these equations become much more complicated because linkage disequilibria measuring associations among alleles from all subsets of loci enter the dynamics. Naturally, these multilocus linkage disequilibria are more complicated than D_α.

Instead of gamete frequencies it is sometimes more convenient to work with allele frequencies and the LD measures D_α. From (10.7) and (10.8), we obtain

$$p_{ij,\alpha} = p^{(1)}_{i,\alpha} p^{(2)}_{j,\alpha} + (-1)^{i+j} D_\alpha\,. \tag{10.19}$$

The constraints $p_{ij,\alpha} \geq 0$ and $\sum_i p_{i,\alpha} = 1$ are transformed to $0 \leq p^{(n)}_{i,\alpha} \leq 1$ and

$$-\min\left\{p^{(1)}_{1,\alpha}p^{(2)}_{1,\alpha}, p^{(1)}_{2,\alpha}p^{(2)}_{2,\alpha}\right\} \leq D_\alpha \leq \min\left\{p^{(1)}_{1,\alpha}p^{(2)}_{2,\alpha}, p^{(1)}_{2,\alpha}p^{(2)}_{1,\alpha}\right\}. \tag{10.20}$$

Appropriate summation in (10.18b) con rms the biologically obvious fact that the change of allele frequencies is una ected by recombination:

$$p^{(1)\#}_{i,\alpha} = \sum_j p_{ij,\alpha}\frac{w_{ij,\alpha}}{w_\alpha}\,, \quad p^{(2)\#}_{j,\alpha} = \sum_i p_{ij,\alpha}\frac{w_{ij,\alpha}}{w_\alpha}\,. \tag{10.21}$$

Let

$$_{0,\alpha} = \{p_{\cdot,\alpha} : D_\alpha = 0\} \subseteq S_4 \tag{10.22}$$

denote the *linkage-equilibrium manifold* in deme α, and let

$$_0 = \quad _{0,1} \times \ldots \times \quad _{0,\Gamma} \subseteq \mathsf{S}_4^\Gamma \,. \tag{10.23}$$

We will often need the following assumption:

The backward migration matrix M is ergodic, i.e., irreducible and aperiodic. (E)

Given irreducibility, the biologically trivial condition that individuals have positive probability of remaining in some deme, i.e., $m_{\alpha\alpha} > 0$ for some α, su ces for aperiodicity (Feller 1968, p. 426). Because M is a nite matrix, ergodicity is equivalent to primitivity.

If (E) holds, there exists a principal left eigenvector $\xi \in \operatorname{int} \mathsf{S}_\Gamma$ such that

$$\xi^\top M = \xi^\top \,. \tag{10.24}$$

The corresponding principal eigenvalue 1 of M is simple and exceeds every other eigenvalue in modulus. The principal eigenvector ξ is the unique stationary distribution of the Markov chain with transition matrix M, and M^n converges at a geometric rate to $e\xi^\top$ as $n \to \infty$, where $e = (1, \ldots, 1)^\top \in \mathbb{R}^\Gamma$. More precisely, let λ_1 denote the nonunit eigenvalue of M with largest modulus. Then the convergence theorem for ergodic matrices (Feller 1968, p. 393; Seneta 1981, p. 9; or Appendix A.2) implies that for every κ with

$$|\lambda_1| < \kappa < 1 \,, \tag{10.25}$$

we have

$$\left\| M^t z - e\xi^\top z \right\| \le c_z \kappa^t \,, \tag{10.26}$$

where c_z is independent of t. If λ_1 is a simple eigenvalue (which it is generically), we can take $\kappa = |\lambda_1|$.

For vectors $y, z \in \mathbb{R}^\Gamma$, we denote the componentwise (Schur) product of y and z by

$$y \circ z = (y_1 z_1, \ldots, y_\Gamma z_\Gamma)^T \,. \tag{10.27}$$

We average the gamete and the allele frequencies with respect to ξ:

$$P_{ij} = \xi^\top p_{ij} \in \mathbb{R} \,, \quad P = (P_{11}, P_{12}, P_{21}, P_{22})^\top \in \mathsf{S}_4 \,, \tag{10.28}$$

$$P_i^{(n)} = \xi^\top p_i^{(n)} \in \mathbb{R} \,, \tag{10.29}$$

where the superscript $^{(n)}$ indicates locus $n \in \{1, 2\}$.

Finally, we define the following deviations from the spatially averaged frequencies:

$$\mathfrak{p}_{ij,\alpha} = p_{ij,\alpha} - P_{ij}\,, \tag{10.30a}$$

$$\mathfrak{p}_{\cdot,\alpha} = p_{\cdot,\alpha} - P \in \mathbb{R}^4\,, \tag{10.30b}$$

$$\mathfrak{p} = (\mathfrak{p}_{\cdot,1}^\top, \ldots, \mathfrak{p}_{\cdot,\Gamma}^\top)^\top \in \mathbb{R}^{4\Gamma}\,, \tag{10.30c}$$

$$\mathfrak{p}_i^{(n)} = p_i^{(n)} - P_i^{(n)} e \in \mathbb{R}^\Gamma\,. \tag{10.30d}$$

Therefore, $\mathfrak{p}$ measures spatial heterogeneity or diversity among subpopulations. If $\mathfrak{p} = 0$, the gametic distribution is spatially homogeneous.

10.3.2 The continuous-time dynamics

Formally, the continuous-time version of the recurrence equations (10.18) can be obtained by assuming that all evolutionary forces are weak. More precisely, we assume that there are constants $s_{ij,k\ell;\alpha}$, ρ, and $\mu_{\alpha\beta}$, such that

$$w_{ij,k\ell;\alpha} = 1 + \epsilon s_{ij,k\ell;\alpha}\,, \quad r = \epsilon\rho\,, \quad m_{\alpha\beta} = \delta_{\alpha\beta} + \epsilon\mu_{\alpha\beta}\,, \tag{10.31}$$

and $\rho \geq 0$ and $\mu_{\alpha\beta} \geq 0$ if $\alpha \neq \beta$. By rescaling time ($t = \lfloor \tau/\epsilon \rfloor$) and letting $\epsilon \to 0$, one obtains the following differential equations for the evolution of gamete frequencies in deme α can be derived straightforwardly:

$$\underline{p}_{ij,\alpha} = p_{ij,\alpha}(s_{ij,\alpha} - s_\alpha) + (-1)^{i+j}\rho D_\alpha + \sum_\beta \mu_{\alpha\beta} p_{ij,\beta}; \tag{10.32}$$

cf. Sections 2.4 and 6. We note that $\sum_\beta \mu_{\alpha\beta} = 0$ for every α, whence the largest eigenvalue of the matrix $L = (\mu_{\alpha\beta})$ is 0 (because $L + I$ is stochastic). In vector form, (10.32) becomes

$$\underline{p}_{ij} = p_{ij} \circ (s_{ij} - s) + (-1)^{i+j}\rho D + L p_{ij}\,. \tag{10.33}$$

Here, selection, recombination, and migration are decoupled. Nevertheless, (10.33) may exhibit complex dynamical behavior if either migration or recombination are absent (Sections 6 and 10.2).

Example 10.1. If fitnesses are additive, i.e., if $s_{ij,k\ell;\alpha} = u_{ik,\alpha} + u_{j\ell,\alpha}$, then $s_{ij,\alpha} = u_{ij,\alpha} + u_\alpha$, $s_\alpha = 2u_\alpha$, where $u_\alpha = \sum_{ij} u_{ij} p_{ij}$. Hence, $s_{ij,\alpha} - s_\alpha = u_{ij,\alpha} - u_\alpha$. If, in addition, at every locus there is no dominance, i.e., if $u_{ij,\alpha} = v_{i,\alpha}^{(1)} + v_{j,\alpha}^{(2)}$, then $u_\alpha = v_\alpha^{(1)} + v_\alpha^{(2)}$, where $v_\alpha^{(n)} = \sum_i v_{i,\alpha}^{(n)} p_{i,\alpha}^{(n)}$. It follows that

$$s_{12,\alpha} - s_\alpha = p_{2,\alpha}^{(1)}(v_{1,\alpha}^{(1)} - v_{2,\alpha}^{(1)}) + p_{1,\alpha}^{(2)}(v_{2,\alpha}^{(2)} - v_{1,\alpha}^{(2)})\,, \tag{10.34}$$

and analogous expressions apply to the fitness deviations of the other gametes.

10.3.3 Migration and recombination

We first study migration and recombination in the absence of selection, i.e., if $w_{ij,k\ell;\alpha} = 1$ for every i, j, k, ℓ, α. Then the dynamics (10.18) reduces to

$$p'_{ij,\alpha} = \sum_{\beta} m_{\alpha\beta}(p_{ij,\beta} + (-1)^{i+j} r D_\beta) \,. \tag{10.35}$$

In vector form, i.e., with the notation (10.16a), (10.35) becomes

$$p'_{ij} = M(p_{ij} + (-1)^{i+j} r D) \,, \quad i \in \{1, 2\} \,. \tag{10.36}$$

From (10.33), we observe that the continuous-time version,

$$\dot{p}_{ij} = L p_{ij} + (-1)^{i+j} \rho D \,, \tag{10.37}$$

is even simpler because migration and recombination are decoupled.

If $r = 0$ the dynamics of the gamete frequencies are decoupled and the convergence theorem for ergodic matrices implies that solutions $p_{ij}(t)$ of (10.36) converge to the constant vector $P_{ij} e$ at the geometric rate κ. An analogous result holds for (10.37) if $\rho > 0$, where it is sufficient to posit that L is irreducible.

The following theorem shows that in the absence of selection trajectories quickly approach linkage equilibrium and spatial homogeneity.

Theorem 10.2. *Suppose* (10.36)*,* $r > 0$*, and* (E) *hold. Then the manifold*

$$\Gamma_0 = \{p \in \Gamma_4 : D = 0 \text{ and } \mathcal{P} = 0\} = \{p \in \Gamma_4 : D = 0 \text{ and } \mathcal{P}_1^{(1)} = \mathcal{P}_1^{(2)} = 0\} \tag{10.38}$$

is invariant under (10.36) *or* (10.37) *and globally attracting at a uniform geometric rate. Furthermore, every point on* Γ_0 *is an equilibrium point.*

This theorem generalizes the well known fact that in two-locus (and in fact in multilocus) systems in which recombination is the only evolutionary force, linkage disequilibria decay to zero at a geometric rate. In contrast to the multilocus case (Bürger 2009a), the proof for two loci is simple. An analogous theorem holds for (10.37) if $\rho > 0$ and L is irreducible.

Proof. In the absence of selection, the recursion equations for the allele frequencies simplify to

$$p_i^{(n)\prime} = M p_i^{(n)} \tag{10.39}$$

for $i, n \in \{1, 2\}$. This implies in particular that the average allele frequencies $P_i^{(n)} = \xi^\top p_i^{(n)}$ remain constant, whence we write $P_i^{(n)} = P_i^{(n)}(0)$. Therefore, (10.26) implies that the allele frequencies $p_i^{(n)}(t)$ converge geometrically to $P_i^{(n)} e$ at rate κ. Hence, every ω-limit is contained in the set $\tilde{}_0 = \{p : p_i^{(n)} = 0$ for every i and $n\}$.

Appealing to $D_\alpha = p_{11,a} - p_{1,\alpha}^{(1)} p_{1,\alpha}^{(2)}$, the recursion equation for LD becomes

$$D' = (1 - r)MD + M\big(p_1^{(1)} \circ p_1^{(2)}\big) - Mp_1^{(1)} \circ Mp_1^{(2)}\,. \tag{10.40}$$

Because of the convergence of allele frequencies to spatial uniformity, it is sufficient to study (10.40) on $\tilde{}_0$, where it simplifies to

$$D' = (1 - r)MD \tag{10.41}$$

since $p_i^{(n)} = P_i^{(n)} e$ is a constant vector, hence a right eigenvector of M pertaining to the leading eigenvalue 1. Obviously, (10.41) implies geometric convergence of D to 0 at rate $1 - r$. This proves the theorem for the discrete-time case and shows that the rate of convergence to $_0$ is $\min\{1 - r, \kappa\}$. □

Remark 10.3. Theorem 10.2 does neither hold for the discrete-time nor the continuous-time model if the migration matrix is reducible. If, for instance, $M = \begin{pmatrix} 1 & 0 \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$, then an allele that is initially absent in the second deme will be also absent at equilibrium, whereas its frequency can be positive in the first deme. In addition, Theorem 10.2 does not hold for the discrete-time model if the migration matrix is periodic. If $M = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$, then each generation the gamete frequencies are swapped between the demes. In both cases, convergence to p = 0 will in general not occur.

10.4 Limiting cases and perturbation results

In the following, we investigate several limiting cases in which useful general results can be proved and perturbation theory allows important extensions. perturbation.

10.4.1 Weak selection

We assume that selection is weaker than recombination and migration. The main result is that all trajectories converge to an invariant manifold $_\epsilon$ close to $_0$ (10.38), on which there is LE and allele frequencies are deme independent. On $_\epsilon$, the dynamics can be described by a small perturbation of a gradient system. This implies that all trajectories converge, i.e., no cycling can occur, and the equilibrium structure can be inferred.

Throughout this section, we assume (E), i.e., the backward migration matrix is ergodic. We assume that there are constants $s_{ij,\alpha} \in \mathbb{R}$ such that

$$w_{ij,k\ell;\alpha} = 1 + \epsilon s_{ij,k\ell;\alpha}\,, \tag{10.42}$$

where $\epsilon \geq 0$ is sufficiently small and $|s_{ij,k\ell;\alpha}| \leq 1$. Migration rates $m_{\alpha\beta}$ and recombination rate r are fixed, so that fitness differences are small compared with them. From (10.17) and (10.42), we deduce

$$w_{ij,\alpha}(p_{\cdot,\alpha}) = 1 + \epsilon s_{ij,\alpha}(p_{\cdot,\alpha})\,, \quad w_\alpha(p_{\cdot,\alpha}) = 1 + \epsilon s_\alpha(p_{\cdot,\alpha})\,, \tag{10.43}$$

in which

$$s_{ij,\alpha}(p_{\cdot,\alpha}) = \sum_{k,\ell} s_{ij,k\ell;\alpha} p_{k\ell,\alpha}\,, \quad s_\alpha(p_{\cdot,\alpha}) = \sum_{i,j,k,\ell} s_{ij,k\ell;\alpha} p_{ij,\alpha} p_{k\ell,\alpha}\,. \tag{10.44}$$

When selection is dominated by migration and recombination, we expect that linkage disequilibria within demes as well as gamete- and gene-frequency differences between demes decay rapidly to small quantities. In particular, we expect approximately panmictic evolution of suitably averaged gamete frequencies in quasi-linkage equilibrium. We also show that all trajectories converge to an equilibrium point, i.e., no complicated dynamics, such as cycling, can occur. In the absence of migration, this was proved by Nagylaki et al. (1999, Theorem 3.1). For a single locus under selection and strong migration, this is the content of Theorem 4.5 in Nagylaki and Lou (2007). Theorem 10.4 and its proof combine and extend these results as well as the underlying ideas and methods.

To formulate and prove this theorem, we define the vector

$$\rho_\alpha = (p^{(1)}_{1,\alpha}, p^{(1)}_{2,\alpha}, p^{(2)}_{1,\alpha}, p^{(2)}_{2,\alpha})^\top \in \mathsf{S}_2^2 \tag{10.45}$$

of allele frequencies at each locus in deme α, and the vector

$$\pi = (P^{(1)}_1, P^{(1)}_2, P^{(2)}_1, P^{(2)}_2)^\top \in \mathsf{S}_2^2 \tag{10.46}$$

of averaged allele frequencies at every locus. We note that because $p^{(n)}_{1,\alpha} + p^{(n)}_{2,\alpha} = 1$, $p^{(1)}_{1,\alpha}$ and $p^{(2)}_{1,\alpha}$ are sufficient to determine ρ_α. Analogously, $P^{(1)}_1$ and $P^{(2)}_1$ determine π.

Importantly, in the presence of selection $P^{(n)}_i$, hence π, is time dependent. Instead of p, we will often use π, D, and $\mathcal{p}$ to analyze (10.18).

On the LE manifold $\mathcal{M}_{0,\alpha}$ (10.22), which is characterized by the ρ_α ($\alpha \in \mathsf{G}$), the selection coefficients of gamete ij and of the entire population are

$$s_{ij,\alpha}(\rho_\alpha) = \sum_{k,\ell} s_{ij,k\ell;\alpha} p^{(1)}_{i,\alpha} p^{(2)}_{j,\alpha}\,, \tag{10.47a}$$

$$s_\alpha(\rho_\alpha) = \sum_{i,j} s_{ij,\alpha}(\rho_\alpha) p^{(1)}_{i,\alpha} p^{(2)}_{j,\alpha}\,, \tag{10.47b}$$

and the selection coe cients of alleles are

$$s^{(1)}_{i,\alpha}(\rho_\alpha) = \sum_j s_{ij,\alpha}(\rho_\alpha) p^{(2)}_{j,\alpha}\,, \quad s^{(2)}_{i,\alpha}(\rho_\alpha) = \sum_j s_{ji,\alpha}(\rho_\alpha) p^{(1)}_{j,\alpha}\,, \tag{10.47c}$$

cf. (10.44). As in (10.24), let ξ denote the principal left eigenvector of M. We introduce the average selection coe cients of diploid genotypes, gametes, and of the entire population:

$$\omega_{ij,k\ell;\alpha} = \sum_\alpha \xi_\alpha s_{ij,k\ell;\alpha}\,, \tag{10.48a}$$

$$\omega_{ij}(\pi) = \sum_{k,\ell} \omega_{ij,k\ell} P^{(1)}_k P^{(2)}_\ell = \sum_\alpha \xi_\alpha s_{ij,\alpha}(\pi)\,, \tag{10.48b}$$

$$\omega(\pi) = \sum_{i,j} \omega_{ij}(\pi) P^{(1)}_i P^{(2)}_j = \sum_\alpha \xi_\alpha s_\alpha(\pi)\,. \tag{10.48c}$$

The average allelic selection coe cients are

$$\omega^{(1)}_i(\pi) = \sum_j \omega_{ij}(\pi) P^{(2)}_j = \sum_\alpha \xi_\alpha s^{(1)}_{i,\alpha}(\pi)\,, \tag{10.48d}$$

$$\omega^{(2)}_i(\pi) = \sum_j \omega_{ji}(\pi) P^{(1)}_j = \sum_\alpha \xi_\alpha s^{(2)}_{i,\alpha}(\pi)\,. \tag{10.48e}$$

For ω, we obtain the alternative representations

$$\omega(\pi) = \sum_n \sum_i \omega^{(n)}_i P^{(n)}_i\,, \tag{10.48f}$$

and

$$\frac{\mathrm{d}\omega(\pi)}{\mathrm{d}P^{(n)}_i} = 2\omega^{(n)}_i(\pi)\,. \tag{10.49}$$

For reasons that will be justi ed by the following theorem, we call the di erential equation

$$\dot{P}^{(n)}_i = P^{(n)}_i \left[\omega^{(n)}_i(\pi) - \omega(\pi)\right]\,, \tag{10.50a}$$

$$D = 0\,,\ p = 0 \tag{10.50b}$$

on S^Γ_4 the *weak-selection limit* of (10.18). In view of the following theorem, it is more convenient to consider (10.50a) and (10.50b) on S^Γ_4 instead of (10.50a) on S^2_2. The di erential equation (10.50a) is a Svirezhev-Shashahani gradient (Remark 2.3) with potential function ω. In particular, ω increases strictly along nonconstant solutions of (10.50a) because

$$\dot{\omega} = 2 \sum_n \sum_i P^{(n)}_i \left[\omega^{(n)}_i(\pi) - \omega(\pi)\right]^2 \geq 0\,. \tag{10.51}$$

We will also need the assumption

All equilibria of (10.50a) are hyperbolic. (H)

Theorem 10.4 (Bürger 2009a). *Suppose that* (10.18), (10.42), (E) *and* (H) *hold, the backward migration matrix* M *and all recombination rates* c_K *are fixed, and* $\epsilon > 0$ *is sufficiently small.*

(a) The set of equilibria $_0 \subset S_4^\Gamma$ *of* (10.50) *contains only isolated points, as does the set of equilibria* $_\epsilon \subset S_4^\Gamma$ *of* (10.18). *As* $\epsilon \to 0$, *each equilibrium in* $_\epsilon$ *converges to the corresponding equilibrium in* $_0$.

(b) In the neighborhood of each equilibrium in $_0$, *there exists exactly one equilibrium point in* $_\epsilon$. *The stability of each equilibrium in* $_\epsilon$ *is the same as that of the corresponding equilibrium in* $_0$*; i.e., each pair is either asymptotically stable or unstable.*

(c) Every solution $p(t)$ *of* (10.18) *converges to one of the equilibrium points in* $_\epsilon$.

An analogous theorem holds for the continuous-time model (10.33) if L is hyperbolic and irreducible.

The essence of this theorem and its proof is that under weak selection (i) the exact dynamics quickly leads to spatial quasi-homogeneity and quasi-linkage equilibrium, and (ii) after this time, the exact dynamics can be perceived as a perturbation of the weak-selection limit (10.50). The latter is much easier to study because it is formally equivalent to a panmictic one-locus selection dynamics. Theorem 10.4 is a singular perturbation result because in the absence of selection every point on $_0$ is an equilibrium.

Parts (a) and (b) of the above theorem follow immediately from Theorem 4.4 of Karlin and McGregor (1972b) which, essentially, is an application of the implicit function theorem and the Hartman-Grobman theorem. Part (c) is much stronger and relies, among others, on the notion of chain-recurrent points and their properties under perturbations of the dynamics (see Section 6). The reason is that hyperbolicity of all equilibria does not exclude the existence of limit cycles or of more complicated dynamics.

Outline of the proof of Theorem 7.3. Theorem 10.2 and the theory of normally hyperbolic manifolds imply that for sufficiently small ϵ, there exists a smooth invariant manifold $_\epsilon$ close to $_0$, and $_\epsilon$ is globally attracting for (10.18) at a geometric rate (see Nagylaki et al. 1999, and the references there). The manifold $_\epsilon$ is characterized by an equation of the form

$$(D, q) = \epsilon\psi(\pi, \epsilon), \tag{10.52}$$

where ψ is a smooth function of π. Thus, on $\quad_\epsilon$, and more generally, for any initial values, after a long time,

$$D(t) = O(\epsilon) \quad \text{and} \quad p(t) = O(\epsilon)\,. \tag{10.53}$$

The next step consists in deriving the recurrence equations in an $O(\epsilon)$ neighborhood of $\quad_0$ which, in particular, contains $\quad_\epsilon$. By applying (10.42) and $D(t) = O(\epsilon)$ to (10.18b), some calculations yield

$$p_{i,\alpha}^{(n)\#} = p_{i,\alpha}^{(n)} + \epsilon p_{i,\alpha}^{(n)} \frac{s_{i,\alpha}^{(n)}(\rho_\alpha) - s_\alpha(\rho_\alpha)}{w_\alpha(\rho_\alpha)} + O(\epsilon^2) \tag{10.54}$$

for every $\alpha \in G$ (see eq. (3.10) in Nagylaki et al. 1999). By averaging, invoking (10.18), (10.54), and (10.52) one obtains

$$\begin{aligned} P_i^{(n)\prime} &= \mu^T p_i^{(n)\prime} = \mu^T M p_i^{(n)\#} = \mu^T p_i^{(n)\#} \\ &= P_i^{(n)} + \epsilon P_i^{(n)} \left[\omega_i^{(n)}(\pi) - \omega(\pi)\right] + O(\epsilon^2)\,. \end{aligned} \tag{10.55}$$

By rescaling time as $\tau = \epsilon t$ and letting $\epsilon \to 0$, the leading term in (10.55), $P_i^{(n)\prime} = P_i^{(n)} + \epsilon P_i^{(n)} \left[\omega_i^{(n)}(\pi) - \omega(\pi)\right]$, approximates the gradient system (10.50a). Therefore, we have $\omega(\pi') > \omega(\pi)$ unless $\pi' = \pi$. In particular, the dynamics (10.55) on $\quad_0$ is gradient like.

The eigenvalues of the Jacobian of (10.55) have the form $1 + \epsilon\nu + O(\epsilon^2)$, where ν signifies an eigenvalue of the Jacobian of (10.50a). Therefore, (H) implies that also every equilibrium of (10.55) is hyperbolic.

The rest of the proof is identical to that of Theorem 3.1 in Nagylaki et al. (1999). The heart of its proof is the following. Since solutions of (10.18) are in phase with solutions on the invariant manifold $\quad_\epsilon$, it is sufficient to prove convergence of trajectories for initial conditions $p \in \quad_\epsilon$. With the help of the qualitative theory of numerical approximations, it can be concluded that the chain-recurrent set of the exact dynamics (10.18) on $\quad_\epsilon$ is a small perturbation of the chain-recurrent set of (10.50a). The latter dynamics, however, is gradient like. Because all equilibria are hyperbolic by assumption, the chain-recurrent set consists exactly of those equilibria. Therefore, the same applies to the chain-recurrent set of (10.18) if $\epsilon > 0$ is small.

A final point to check is that unstable boundary equilibria remain in the state space after perturbation. The reason is that an equilibrium $\hat{p}$ of (10.50) on the boundary of S_4^Γ satisfies $\hat{p}_{ij} = 0$ for every gamete ij ($i, j \in \{1, 2\}$), and this condition is not altered by migration. The positive components of $\hat{p}$ are perturbed within the boundary, where the equilibrium remains. □

Our next result concerns the average of the (exact) mean tnesses over demes:

$$w(p) = \sum_{\alpha} \xi_\alpha w_\alpha(p_{\cdot,\alpha}) \,. \tag{10.56}$$

Theorem 10.5 (Burger 2009a). *Suppose the assumptions of Theorem 10.4 apply. If* (10.53) *holds, π is bounded away from the equilibria of* (10.50a)*, and p is within $O(\epsilon^2)$ of $_\epsilon$, then $w(p) > 0$.*

An essential step in the proof is to show that

$$(D', q') - (D, q) = O(\epsilon^2) \tag{10.57}$$

is satis ed if (10.53) holds. Therefore, linkage disequilibria and the measure q of spatial diversity change very slowly on $_\epsilon$. This justi es to call states on $_\epsilon$ spatially quasi-homogeneous and to be in quasi-linkage equilibrium.

Theorem 10.4 enables the derivation of the following result about the equilibrium structure of the multilocus migration-selection dynamics (10.18). It establishes that arbitrarily many loci with arbitrarily many alleles can be maintained polymorphic by migration-selection balance:

Theorem 10.6. *Let ≥ 2 and $r > 0$.*

(a) There exists an open set Q *of migration and selection parameters, such that for every parameter combination in* Q*, there is a unique, internal, asymptotically stable equilibrium point. This equilibrium is spatially quasi-homogeneous, is in quasi-linkage equilibrium, and attracts all trajectories with internal initial condition. Furthermore, every trajectory converges to an equilibrium point as $t \to \infty$.*

(b) Such an open set, Q′*, also exists if the set of all fitnesses is restricted to be nonepistatic and to display intermediate dominance.*

For a more detailed formulation and a proof, see Theorem 2.2 in Burger (2009b). The constructive proof suggests that with increasing number of alleles and loci, the proportion of parameter space that allows for a fully polymorphic equilibrium shrinks very rapidly because at each locus some form of overdominance of spatially averaged tnesses is required. In addition, the proof shows that this set Q exists in the parameter region where migration is strong relative to selection.

If selection is nonepistatic and su ciently weak relative to migration and recombination, and if all one-locus tnesses are multiplicative or additive (or, more generally, if there is DIDID (5.27)), then one gamete becomes xed as $t \to \infty$ (Proposition 2.6 in Burger 2009b).

10.4.2 Strong migration

Now we assume that selection and recombination are weak relative to migration, i.e., in addition to (10.42), we posit

$$r = \epsilon\rho\,, \tag{10.58}$$

where $\epsilon \geq 0$ is sufficiently small and ρ is defined by this relation. Then every solution $p(t)$ of the full dynamics (10.18) converges to a manifold close to $\dot{p} = 0$. On this manifold, the dynamics is approximated by the differential equation

$$\dot{P}_{ij} = P_{ij}[\omega_{ij}(P) - \omega(P)] - \rho\left[P_{ij} - P_i^{(1)}P_j^{(2)}\right]\,, \tag{10.59a}$$

which we augment with

$$\dot{p} = 0\,. \tag{10.59b}$$

This is called the *strong-migration limit* of (10.18).

In general, it cannot be expected that the asymptotic behavior of solutions of (10.18) under strong migration is governed by (10.59) because its chain-recurrent set does not always consist of finitely many hyperbolic equilibria. The differential equation (10.59a) is the continuous-time version of the discrete-time dynamics (10.18b) which describes evolution in a panmictic population subject to multilocus selection and recombination. Although the recombination term is much simpler than in the corresponding difference equation, the dynamics is not necessarily less complex. Akin (1979, 1982) proved that (10.59) may exhibit stable cycling. Therefore, under strong migration and if selection and recombination are about equally weak, convergence of trajectories of (10.18) will not generally occur, and only local perturbation results can be derived (Bürger 2009a, Proposition 4.10).

The dynamics (10.59) becomes simple if there is no epistasis. Then mean fitness is a Lyapunov function, all equilibria are in linkage equilibrium, and global convergence of trajectories occurs generically (Ewens 1969, Lyubich 1992, Nagylaki et al. 1999).

10.4.3 Weak recombination

If recombination is weak relative to migration and selection, the limiting dynamics is formally equivalent to a one-locus migration-selection model. These are the models treated in Sections 3 – 9.

10.4.4 Weak migration

In contrast to the one-locus case (Sect. 7), in the multilocus case the assumption of weak migration is insu cient to guarantee convergence of all trajectories to equilibrium. The reason is that in the absence of migration the dynamics (10.18) reduces to

$$p'_{ij,\alpha} = p^{\#}_{ij,\alpha} = p_{ij,\alpha}\frac{w_{ij,\alpha}}{w_\alpha} + (-1)^{i+j} r D_\alpha \tag{10.60}$$

for every gamete ij and every $\alpha \in G$ (10.18b). Therefore, we have decoupled multilocus selection dynamics, one for each deme. Because already for a single deme, stable cycling has been established (Hastings 1981, Hofbauer and Iooss 1984), global perturbation results can not be achieved without additional assumptions. Such an assumption is that of weak epistasis.

10.4.5 Weak migration and weak epistasis

In addition to weak migration, i.e., (7.1) and (7.2), we assume weak epistasis. The latter means that we can assign (constant) tness components $u^{(n)}_{i_n j_n,\alpha} > 0$ to single-locus genotypes, such that we can write

$$w_{ij,k\ell;\alpha} = \sum_n u^{(n)}_{i_n j_n,\alpha} + \eta s_{ij,\alpha}\,, \tag{10.61}$$

where the numbers $s_{ij,\alpha}$ satisfy $|s_{ij,\alpha}| \le 1$ and $\eta \ge 0$ is a measure of the strength of epistasis. It is always assumed that η is small enough that $w_{ij,k\ell;\alpha} > 0$. Throughout the following, we posit

$$\eta = \eta(\epsilon)\,, \tag{10.62}$$

where $\eta : [0,1) \to [0,\infty)$ is C^1 and satis es $\eta(0) = 0$. Therefore, migration and epistasis need not be `equally' weak. In particular, the case $\eta \equiv 0$, i.e., no epistasis, is included.

In the absence of epistasis and migration ($\epsilon = \eta = 0$), p is an equilibrium point of (10.60) if and only if for every $\alpha \in G$, $p_{\cdot,\alpha}$ is both a selection equilibrium for each locus and is in linkage equilibrium. In addition, the only chain-recurrent points of (10.60) are its equilibria (Lemmas 2.1 and 2.2 in Nagylaki et al. 1999). Therefore, one can apply the proof of Theorem 2.3 in Nagylaki et al. (1999), to deduce the following result which simultaneously generalizes Theorem 2.3 in Nagylaki et al. (1999) and Theorem 7.3:

Theorem 10.7 (Bürger 2009a, Theorem 5.4). *Suppose that in the absence of epistasis every equilibrium of* (10.60) *is hyperbolic, and* $\epsilon > 0$ *(and* $\eta > 0$*) are sufficiently small.*

(a) The set of equilibria $_0 \subset S_4^\Gamma$ *of* (7.3) *contains only isolated points, as does the set of equilibria* $_\epsilon \subset S_4^\Gamma$ *of* (10.18)*. As* $\epsilon \to 0$*, each equilibrium in* $_\epsilon$ *converges to the corresponding equilibrium in* $_0$*.*

(b) In the neighborhood of each asymptotically stable equilibrium in $_0$*, there exists exactly one equilibrium in* $_\epsilon$*, and it is asymptotically stable. In the neighborhood of each unstable internal equilibrium in* $_0$*, there exists exactly one equilibrium in* $_\epsilon$*, and it is unstable. In the neighborhood of each unstable boundary equilibrium in* $_0$*, there exists at most one equilibrium in* $_\epsilon$*, and if it exists, it is unstable.*

(c) Every solution $p(t)$ *of* (10.18) *converges to one of the equilibrium points in* $_\epsilon$*.*

Remark 10.8. (i) Parts (a) and (b) of the above theorem follow immediately from Theorem 4.4 of Karlin and McGregor (1972b) which, essentially, is an application of the implicit function theorem. Part (c) is much stronger and relies, among others, on the notion of chain-recurrent points and their properties under perturbations of the dynamics. The reason is that hyperbolicity of all equilibria does not exclude the existence of limit cycles or of more complicated dynamics; cf. Remark ??.

(ii) In contrast to the case of weak selection (Theorem 10.4), unstable boundary equilibria can leave the state space under weak migration (Karlin and McGregor 1972a). For an explicit example in a single-locus setting, see Remark 4.2 in Nagylaki and Lou (2007).

If $\epsilon = 0$, then all equilibria are in $_0$, i.e., there is linkage equilibrium within each deme, but not between demes. If $\epsilon > 0$ is su ciently small, then there is weak linkage disequilibrium within each deme, i.e., $D_{i,\alpha} = O(\epsilon)$ for every i and every α.

One of the consequences of the above theorem is the following:

Theorem 10.9 (Theorem 3.9 in Bürger 2009b)**.** *For arbitrary number of loci, sufficiently weak migration and epistasis, and partial dominance, the number of demes is the generic maximum for the number of alleles that can be maintained at any locus at any equilibrium (stable or not) of* (10.18)*.*

10.4.6 The Levene model

Many of the results on the one-locus Levene model in Sections 5.1 and 5.2 can be generalized to the multilocus Levene model if epistasis is absent or weak. One key result for this is that, in the absence of epistasis, geometric mean tness is again a Lyapunov function, and the internal equilibria are its stationary points (Theorems 3.2 and 3.3 in Nagylaki 2009b). The other key result is that in the absence of epistasis, generically, every trajectory converges to an equilibrium point that is in LE (Theorem 3.1 in Bürger 2010). Then

a proof analogous to that of Theorem 10.7 yields a global perturbation result for weak epistasis, in particular, generic global convergence to an equilibrium point in quasi-linkage equilibrium (Theorem 7.2 in Bürger 2010).

10.4.7 Comments on the maintenance of genetic variation

Because for a single randomly mating population, polymorphic equilibria cannot exist in the absence of epistasis and of overdominance or underdominance, it is natural to con ne attention to the investigation of the maintenance of genetic variation in subdivided populations if in each subpopulation epistasis is absent and dominance is intermediate. Sections 4.2 and 4.3, Examples 5.16, 5.17, and 6.1, and Theorems 5.18, 5.19, 7.7, 9.1, and 9.8 provide relevant results for the one-locus case, whereas Theorems 10.6 and 10.9 treat multiple loci. Theorem 10.6 establishes that in a subdivided population, migration-selection balance can maintain multiallelic polymorphism at arbitrarily many loci under conditions for which in a panmictic population no polymorphism at all can be maintained. These conditions are no or weak epistasis and intermediate levels of dominance at every locus (and in every deme).

Interestingly, for strong migration and only two demes, an arbitrary number of alleles can be maintained at each of arbitrarily many loci, whereas for weak migration, the number of demes is a generic upper bound for the number of alleles that can be maintained (Theorem 10.9). At rst, this contrast appears counterintuitive given the frequently expressed opinion that, in general, it is easier to maintain polymorphism under weak migration than under strong migration. This opinion derives from the fact that for a single diallelic locus and two demes, the parameter region for which a protected polymorphism exists increases with decreasing migration rate, as is immediate from the conditions for protection, (4.13), (4.14), and (4.15). Additional support for this expectation comes from the study of weak migration in homogeneous and heterogeneous environments (Karlin and McGregor 1972a,b; Christiansen 1999), from the analysis of the Deakin (1966) model (Sect. 4.3, as well as from various numerical studies (e.g., Spichtig and Kawecki 2004, Star et al. 2007a,b). In contrast, Karlin (1982, p. 128) noted that for the non-homogeneous Deakin model, in which the `homing probabilities' vary among demes, \it is possible to increase a single homing rate and reduce or even abrogate the event of A-protection".

Theorem 10.6 is not at variance with those just mentioned, but is complimentary. It yield a deeper understanding of the conditions under which variation can be maintained by migration-selection balance. With strong migration, a stable multiallelic polymorphism

requires some form of overdominance at this locus for suitably averaged tnesses. The reason is that strong migration leads to strong mixing, so that gamete and allele frequencies become similar among demes. Therefore, we expect that the constraints on selection for maintaining multilocus polymorphism under strong migration are quite stringent, i.e., some form of average overdominance is indispensable.

The conditions for maintaining loci polymorphic under weak migration are much weaker. With arbitrary intermediate dominance, the proof of Theorem 10.9 shows that for the maintenance of all alleles it is essentially su cient that at each locus every allele is the ttest in at least one niche. This, obviously, limits the number of alleles that can be maintained.

Also in the Levene model arbitrarily many loci can be maintained polymorphic in the absence of epistasis and if dominance is intermediate in every deme. But there, the maximum number of polymorphic loci depends on the pattern of dominance and the number of demes (Nagylaki 2009b, Bürger 2010). It is an open problem if for every (ergodic) migration scheme, arbitrarily many loci can be maintained polymorphic in the absence of epistasis and of overdominance and underdominance.

Although the range of parameters, in which the conditions for maintenance of multiallelic multilocus polymorphisms are satis ed, decreases rapidly in proportion to the full parameter space as the number of alleles or loci increases, for a small or moderate number of alleles or loci, stable multiallelic polymorphism does not seem unlikely. What is required if dispersal is weak, basically, is that there is a mosaic of directional selection pressures and di erent genes or genotypes that are locally well adapted.

10.5 Evolution of Dobzhansky-Muller incompatibilities with gene flow

This is based on Bank et al. (2012). A pdf of the slides can be obtained on request.

A Appendix

In this appendix, we summarize important mathematical methods and results that are useful tools in the analysis of population genetics models.

A.1 Basics from dynamical systems

The study of the evolution of gene frequencies requires the mathematical investigation of di erence or di erential equations that describe gene-frequency change across generations. Here, we summarize the basic concepts needed for exploring the dynamical and equilibrium properties of solutions of such equations. A concise introduction, focused on stability of di erence and di erential equations, is LaSalle's (1976) text. Hofbauer and Sigmund (1998) develop the theory of dynamical systems hand in hand with topics from evolutionary biology.

A.1.1 Difference equations

Let $\mathbb{R}^k$ denote the k-dimensional Euclidean space and let X be a subset of $\mathbb{R}^k$. A *discrete dynamical system* consists of a map T of X into itself, $\boldsymbol{x} \to T\boldsymbol{x}$, where $\boldsymbol{x}$ is a vector in X. We shall call X the state space. The map T can be iterated, and the sequence $\boldsymbol{x}$, $T\boldsymbol{x}$, $T^2\boldsymbol{x} = T(T\boldsymbol{x}), \ldots, T^n\boldsymbol{x}, \ldots$, is called the *orbit*, or *trajectory*, of $\boldsymbol{x}$. The vector $\boldsymbol{x}$ may be interpreted as the initial state and n as the number of time intervals elapsed. We assume that T is di erentiable. Associated with the map $\boldsymbol{x} \to T\boldsymbol{x}$ is the *difference equation*, or *recursion relation*,

$$\boldsymbol{x}' = T\boldsymbol{x} \ , \tag{A.1}$$

which stands for $\boldsymbol{x}(n+1) = T(\boldsymbol{x}(n))$.

Of primary interest is the behavior of $T^n\boldsymbol{x}$ for large values of n. A point $\boldsymbol{y}$ is a *limit point* (accumulation point) of $T^n\boldsymbol{x}$ if there is a sequence of integers n_i ($n_i \to \infty$) such that $T^{n_i}\boldsymbol{x} \to \boldsymbol{y}$. The *$\omega$-limit* $\omega(\boldsymbol{x})$ of (the orbit $T^n\boldsymbol{x}$ of) $\boldsymbol{x}$ is the set of all limit points of $T^n\boldsymbol{x}$. An orbit $T^n\boldsymbol{x}$ is called *periodic* (or *cyclic*) if for some $k > 0$, $T^k\boldsymbol{x} = \boldsymbol{x}$. The least such integer is the *period* of the cycle. A point $\boldsymbol{x}$ such that $T\boldsymbol{x} = \boldsymbol{x}$ is called an *equilibrium*, a *fixed point*, or a *stationary state*. Frequently, ω-limits consist of periodic orbits or equilibria. To describe the basic properties of ω-limits, we need two further notions. A set H is said to be *positively invariant* if $T(H) \subseteq H$, and *invariant* if $T(H) = H$. Finally, a closed invariant set H is said to be *invariantly connected* if it is not the union of two

nonempty disjoint closed invariant sets. An invariant set with a finite number of elements is invariantly connected if and only if it is a periodic motion.

ω-limits have the following two important properties (LaSalle 1976).

Theorem A.1. *1. Every ω-limit is closed and positively invariant.*

2. If $T^n\boldsymbol{x}$, $n \geq 1$, is bounded, then $\omega(\boldsymbol{x})$ is nonempty, compact, invariant, invariantly connected, and is the smallest closed set that $T^n\boldsymbol{x}$ approaches as $n \to \infty$.

This implies, for example, that if $T^n\boldsymbol{x}$ approaches a set with finitely many elements, $\omega(\boldsymbol{x})$ is a periodic set. In particular, if $T^n\boldsymbol{x}$ converges (i.e., to a single point $\boldsymbol{y}$), then $\boldsymbol{y} = \omega(\boldsymbol{x})$ is an equilibrium.

The central tool for obtaining information about the location of ω-limits are *Lyapunov functions*. Let $V : X \to \mathbb{R}$ and define $\Delta V(\boldsymbol{x}) = V(\boldsymbol{x}') - V(\boldsymbol{x})$. This can be computed without knowing the solution of (A.1). The function V is called a Lyapunov function of (A.1) on a subset $Y \subseteq X$ if (i) V is continuous in $\boldsymbol{x}$ and (ii) $\Delta V(\boldsymbol{x}) \leq 0$ for all $\boldsymbol{x} \in Y$. (Condition (ii) could be replaced by $\Delta V(\boldsymbol{x}) \geq 0$.) We denote by $\overline{Y}$ the closure of Y, i.e., the smallest set containing Y and all of its accumulation points. Now we can formulate an extended version of Lyapunov's invariance principle (LaSalle 1976).

Theorem A.2. *If V is a Lyapunov function of (A.1) on Y and if $T^n\boldsymbol{x}$ is bounded and in Y for every $n \geq 0$, then $\omega(\boldsymbol{x})$ is contained in the maximal invariant subset of $\{\boldsymbol{y} \in \overline{Y} : \Delta V(\boldsymbol{y}) = 0\}$. In particular, there is a number c such that $V(\boldsymbol{y}) = c$ for all $\boldsymbol{y} \in \omega(\boldsymbol{x})$.*

Next we consider questions of stability. A set H is said to be *stable* if, given a neighborhood U of H (i.e., an open set containing the closure $\overline{H}$), there is a neighborhood W of H such that $T^n(W) \subseteq U$ for every $n \geq 0$. This means that any orbit through W remains in U. This is a fairly weak concept of stability. A stronger and more important notion of stability is that of asymptotic stability. First, a set H is an *attractor* if there is a neighborhood U of H such that $x \in U$ implies $\omega(\boldsymbol{x}) \subseteq \overline{H}$. The set H is said to be *asymptotically stable* if it is stable and an attractor. H is called *globally asymptotically stable* if $T^n\boldsymbol{x} \to \overline{H}$ as $n \to \infty$ for all $x \in X$. The *basin of attraction* of a set H is the set of all $\boldsymbol{x}$ such that $\omega(\boldsymbol{x}) \in H$. The following criterion shows how a Lyapunov function can be used to prove (global) asymptotic stability and to obtain estimates for the basin of attraction.

Theorem A.3. *Let Y be a bounded open positively invariant set in X, and denote by M the largest invariant set in $\{\boldsymbol{y} \in \overline{Y} : \Delta V(\boldsymbol{y}) = 0\}$. If (i) V is a Lyapunov function of*

(*A*.1) *on* Y *and* (ii) $M \subset Y$*, then* M *is an attractor and the basin of attraction contains* $\overline{Y}$*. If, in addition,* (iii) V *is constant on* M*, then* M *is asymptotically stable and globally stable relative to* Y*.*

We notice that condition (iii) is automatically satis ed if M is a single point or if M is an invariantly connected set with a nite number of elements. The main di culty in applying the above results consists, of course, in nding an appropriate Lyapunov function. Asymptotic stability can also be inferred by linear approximation of (A.1). Suppose that $\hat{\boldsymbol{x}}$ is an equilibrium of (A.1) and denote by A the $k \times k$ matrix that is the linear approximation to T at $\hat{\boldsymbol{x}}$. Thus, $\mathsf{A} = D_{\boldsymbol{x}}T(\hat{\boldsymbol{x}})$ is the *Jacobian matrix*[6] of T, evaluated at $\hat{\boldsymbol{x}}$. Then (A.1) can be written as

$$\boldsymbol{x}' = \hat{\boldsymbol{x}} + \mathsf{A}(\boldsymbol{x} - \hat{\boldsymbol{x}}) + \boldsymbol{h}(\boldsymbol{x} - \hat{\boldsymbol{x}}) \,, \tag{A.2}$$

where $\boldsymbol{h}(\boldsymbol{x} - \hat{\boldsymbol{x}})$ is the remainder term. Denote by $r(\mathsf{A})$ the spectral radius of A (cf. Appendix B). Then the following holds:

Theorem A.4. *If* $\boldsymbol{h}(\boldsymbol{x})$ *is* $o(\boldsymbol{x})$ *as* $\boldsymbol{x} \to 0$ *and if* $r(\mathsf{A}) < 1$ *(i.e., the modulus of all eigenvalues is less than one), then* $\hat{\boldsymbol{x}}$ *is an asymptotically stable equilibrium of* (*A*.2)*. If* $r(\mathsf{A}) > 1$*, then* $\hat{\boldsymbol{x}}$ *is unstable.*

If no eigenvalue of A has absolute value one, then the equilibrium is called *hyperbolic*. In this case, the orbits of (A.1) near an equilibrium $\hat{\boldsymbol{x}}$ look like those of the linearization $\boldsymbol{x}' = \hat{\boldsymbol{x}} + \mathsf{A}(\boldsymbol{x} - \hat{\boldsymbol{x}})$ near $\hat{\boldsymbol{x}}$. Hyperbolic equilibria are either sinks, sources, or saddles.

A powerful tool to prove that a given function is a Lyapunov function is the following result of Baum and Eagon (1967):

Theorem A.5. *Let* $P(\boldsymbol{x})$ *be a polynomial with nonnegative coefficients, homogeneous of degree* d *in its variables* $x_1, \ldots, x_k$*. Let* $\boldsymbol{x} = (x_1, \ldots, x_k)$ *be any point satisfying* $x_i \geq 0$ *for every* i *and* $\sum_{i=1}^{k} x_i = 1$*, and let* $\boldsymbol{y}(\boldsymbol{x}) = (y_1(\boldsymbol{x}), \ldots, y_k(\boldsymbol{x}))$ *be given by*

$$y_i(\boldsymbol{x}) = x_i \frac{\partial P}{\partial x_i} \Big/ \sum_{j=1}^{k} x_j \frac{\partial P}{\partial x_j} \,. \tag{A.3}$$

Then $P(\boldsymbol{y}(\boldsymbol{x})) > P(\boldsymbol{x})$ *holds unless* $\boldsymbol{y}(\boldsymbol{x}) = \boldsymbol{x}$*.*

[6]For a continuously differentiable map $f : \mathbb{R}^k \to \mathbb{R}^m$ the Jacobian (matrix) $D_{\boldsymbol{x}} f(\boldsymbol{y})$ is the $m \times k$ matrix of first-order partial derivatives $\partial f_i / \partial x_j$ of $f = (f_1, \ldots, f_m)$ evaluated at $\boldsymbol{y}$.

A.1.2 Differential equations

Let Y be an open set in $\mathbb{R}^k$, $f : Y \to \mathbb{R}^k$ a (su ciently often) di erentiable function, and let the state space X be contained in Y. We consider time-independent ordinary di erential equations of the form

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \dot{\boldsymbol{x}} = f(\boldsymbol{x}) \,, \tag{A.4}$$

where $f(\boldsymbol{x}) = (f_1(\boldsymbol{x}), \ldots, f_k(\boldsymbol{x}))$. If for all $\boldsymbol{x} \in X$ and all $t \in \mathbb{R}$, the solution $\boldsymbol{x}(t)$ with $\boldsymbol{x}(0) = \boldsymbol{x}$ is de ned and lies in X, then (A.4) determines a *continuous dynamical system* in X. Many of the concepts and results encountered above for di erence equations possess straightforward analogues for such di erential equations.

To each $\boldsymbol{x} \in X$ corresponds the *orbit* $\{\boldsymbol{x}(t) : t \in \mathbb{R}\}$. Sometimes, one considers semi-dynamical systems de ned only for $t \geq 0$ and *positive semi-orbits* $\{\boldsymbol{x}(t) : t \geq 0\}$. Let $\boldsymbol{x}(t)$ be a solution of (A.4) de ned for all $t \geq 0$, satisfying the initial condition $\boldsymbol{x}(0) = \boldsymbol{x}$. The ω-limit of $\boldsymbol{x}$ is the set of all accumulation points of $\boldsymbol{x}(t)$ for $t \to \infty$, i.e.,

$$\omega(\boldsymbol{x}) = \{\boldsymbol{y} \in \mathbb{R}^n : \boldsymbol{x}(t_k) \to \boldsymbol{y} \text{ for some sequence } t_k \to \infty\} \,. \tag{A.5}$$

The ω-limit may be empty. However, if the positive semi-orbit remains in some compact set, the ω-limit cannot be empty. Every point on the orbit of $\boldsymbol{x}$ has the same ω-limit. A set is called (*positively*) *invariant* if every solution which starts in it remains there for all $t \in \mathbb{R}$ (for all $t \geq 0$). α-limits and negatively invariant sets are de ned in the same way, but for $t \to -\infty$. The following theorem is analogous to Theorem A.1.

Theorem A.6. *1. Every ω-limit is closed and invariant.*

2. If $\boldsymbol{x}(t)$ remains in a compact set for all $t \geq 0$, then $\omega(\boldsymbol{x})$ is nonempty, compact, connected, invariant, and is the smallest closed set that $\boldsymbol{x}(t)$ approaches as $t \to \infty$.

A point $\boldsymbol{x}$ is called an *equilibrium* if $\boldsymbol{x}(t) = \boldsymbol{x}$ for all $t \in \mathbb{R}$. These points are characterized by the condition $f(\boldsymbol{x}) = \boldsymbol{0}$. A point $\boldsymbol{x}$ is called a *periodic point* if $\boldsymbol{x}(\tau) = \boldsymbol{x}(0)$ for some $\tau > 0$, but $\boldsymbol{x}(t) \neq \boldsymbol{x}$ for all $t \in (0, \tau)$. The number τ is called the period. Such a motion describes a periodic oscillation. Equilibria and periodic orbits constitute their own ω-limit.

A continuously di erentiable function $V : Y \to \mathbb{R}$ is called a *Lyapunov function* if V is nondecreasing (or nonincreasing) along orbits, i.e., if the time derivative $\dot{V}$ of the

map $t \to V(\boldsymbol{x}(t))$ satisfies $\dot{V} \geq 0$ (or $\dot{V} \leq 0$). This derivative can be calculated without knowing the solutions, because

$$\dot{V}(\boldsymbol{x}) = \operatorname{grad} V(\boldsymbol{x})^{\top} \dot{\boldsymbol{x}} = \sum_{i=1}^{k} \frac{\partial V(\boldsymbol{x})}{\partial x_i} f_i(\boldsymbol{x}) \;, \tag{A.6}$$

where $\operatorname{grad} V(\boldsymbol{x})$ denotes the gradient vector. Now we formulate a generalization of Lyapunov's invariance principle.

Theorem A.7. *Let S and Y_1 be positively invariant subsets of Y with respect to (A.4) such that $S \subset Y_1 \subseteq Y$.*

1. *If $\dot{V} < 0$ on $Y_1 \setminus S$ (thus V is Lyapunov function on $Y_1 \setminus S$), then for all $\boldsymbol{x} \in Y_1$ the ω-limit $\omega(\boldsymbol{x})$ is contained in S.*

2. *If $\dot{V} \leq 0$ on Y_1, then every such ω-limit is contained in the maximal invariant subset of $\{\boldsymbol{y} \in Y_1 : \dot{V}(\boldsymbol{y}) = 0\}$.*

Proofs and more details may be found in LaSalle (1976) and Hofbauer and Sigmund (1998) (cf. also Bürger 1983b).

For differential equations, the notions of attractor, asymptotic stability, etc. are defined in the same way as for difference equations. Thus, Theorem A.7 provides an important tool for proving global stability of equilibria relative to some subset of the state space.

In many cases the local behavior of solutions near an equilibrium $\hat{\boldsymbol{x}}$ of (A.4) can be determined by studying the approximating linear differential equation

$$\dot{\boldsymbol{x}} = \mathsf{A}\boldsymbol{x} \;, \tag{A.7}$$

where $\mathsf{A} = D_{\boldsymbol{x}} f(\hat{\boldsymbol{x}})$ is the Jacobian matrix of f. In an informal way, the Theorem of Hartman and Grobman states that for any equilibrium $\hat{\boldsymbol{x}}$ of (A.4) that has no eigenvalues on the imaginary axis (such equilibria are called *hyperbolic*), the orbits of (A.4) near $\hat{\boldsymbol{x}}$ look like those of (A.7) near $\mathbf{0}$. In particular, if all eigenvalues of A have (strictly) negative real part, then $\hat{\boldsymbol{x}}$ is (locally) asymptotically stable; the equilibrium $\hat{\boldsymbol{x}}$ is a *saddle* if some eigenvalues are in the left half and some in the right half of the complex plane, but none on the imaginary axis. The orbits whose ω-limit is $\{\mathbf{0}\}$ form a linear submanifold of $\mathbb{R}^k$, called the *stable manifold*; those whose α-limit is $\{\mathbf{0}\}$ form the *unstable manifold*. The local behavior of orbits of (A.4) near equilibria with eigenvalues on the imaginary axis depends on higher-order terms of the Taylor expansion of f.

In population genetics, as well as in several other fields of evolutionary biology, (systems of) differential equations occur, with the simplex S_k as their state space, that are of the form

$$\dot{x}_i = x_i[f_i(\boldsymbol{x}) - f(\boldsymbol{x})] , \quad i = 1, \ldots, k , \tag{A.8}$$

with $f(\boldsymbol{x}) = \sum_{i=1}^{k} x_i f_i(\boldsymbol{x})$. These are called replicator equations (Hofbauer and Sigmund 1998). A typical example is the selection equation in continuous time. Equilibria of such equations are given by the conditions $x_i = 0$ or $f_i(\boldsymbol{x}) = 0$, $i = 1, \ldots, k$. An equilibrium point $\hat{\boldsymbol{x}}$ of (A.8) is called *saturated*, or *externally stable*, if $f_i(\hat{\boldsymbol{x}}) \leq f(\hat{\boldsymbol{x}})$ whenever $\hat{x}_i = 0$. Every equilibrium in the interior of S_k is trivially saturated. For an equilibrium on the boundary, the condition means that if a missing type is introduced at low frequency it will be lost. Typical examples of nonsaturated, or externally unstable, equilibria are the boundary equilibria in the one-locus two-allele selection model with overdominance. If mutation is added to a model like (A.8), then a saturated equilibrium at the boundary will be pushed into the interior of the state space. For a boundary equilibrium $\hat{\boldsymbol{x}}$, $f_i(\hat{\boldsymbol{x}}) - f(\hat{\boldsymbol{x}})$ is an eigenvalue of the Jacobian if $x_i = 0$. It is called a transversal eigenvalue and measures the rate of approach to the face $x_i = 0$ near $\hat{\boldsymbol{x}}$. A boundary equilibrium is saturated if and only if all its transversal eigenvalues are nonpositive (see Hofbauer and Sigmund (1998) for more results).

A.1.3 Gradient systems

A differential equation of the form (A.4) is called a *gradient system* if there exists a function $V : Y \to \mathbb{R}$ with continuous partial second-order derivatives, such that

$$\dot{\boldsymbol{x}} = -\operatorname{grad} V(\boldsymbol{x}) . \tag{A.9}$$

The function V is called the *potential*. Its derivative is

$$D_{\boldsymbol{x}} V(\boldsymbol{y}) = \operatorname{grad} V(\boldsymbol{x})^{\top} \boldsymbol{y} . \tag{A.10}$$

By (A.6) and (A.9), this implies that the time derivative of V along orbits is given by

$$\dot{V}(\boldsymbol{x}) = \operatorname{grad} V(\boldsymbol{x})^{\top} \dot{\boldsymbol{x}} = -\left|\operatorname{grad} V(\boldsymbol{x})\right|^2 . \tag{A.11}$$

Hence, V is a Lyapunov function, and $\dot{V}(\boldsymbol{x}) = 0$ holds if and only if $\boldsymbol{x}$ is an equilibrium. Our next theorem summarizes the basic properties of gradient systems.

Theorem A.8. *1. At regular points* ($\operatorname{grad} V(\boldsymbol{x}) \neq 0$)*, the orbits cross the level surfaces* ($V(\boldsymbol{x}) = const.$) *orthogonally.*

2. *Nonregular points are equilibria.*

3. *The α- and ω-limits of any orbit are critical points* (*where* $\operatorname{grad} V(\boldsymbol{x}) = 0$) *of* V.

4. *Isolated minima of* V *are asymptotically stable.*

5. *The differential equation* $\dot{\boldsymbol{x}} = -f(\boldsymbol{x})$ *is a gradient system if and only if the integrability conditions* $\partial f_i/\partial x_j = \partial f_j/\partial x_i$ *hold for every* i, j. *In particular, the Jacobian matrix* $D_{\boldsymbol{x}} f = (\partial^2 V/(\partial x_i \partial x_j))$ *is symmetric and all eigenvalues at an equilibrium are real.*

A.2 Perron–Frobenius theory of nonnegative matrices

In this appendix we summarize some important results from the spectral theory of nonnegative matrices. These were discovered by Perron and Frobenius around 1910 and are useful tools in proving existence, uniqueness, positivity, and stability of equilibrium solutions in mutation-selection models. For a more complete account of the spectral theory of nonnegative matrices, including proofs, the reader is referred to Gantmacher (1959), Schaefer (1974, Chapter I), or Seneta (1981). The latter reference contains, in particular, a detailed treatment of countably in nite matrices.

A $k \times k$ matrix $A = (a_{ij})$ is called *nonnegative*, $A \geq 0$, if $a_{ij} \geq 0$ for every i, j. It is called *positive*, $A > 0$, if $a_{ij} > 0$ for every i, j. Similarly, a vector $\boldsymbol{x} = (x_1, \ldots, x_k)^\top$ is said to be nonnegative (positive) if $x_i \geq 0$ ($x_i > 0$) for every i.

The *spectral radius* $r = r(A)$ of an arbitrary matrix A is the radius of the smallest circle in the complex plain that contains all eigenvalues of A, i.e., $|\lambda| \leq r$ for all eigenvalues λ of A. It can be shown that $r = \lim_n \|A^n\|^{1/n}$, where $\|A\|$ is an arbitrary norm of the matrix A, e.g., $\|A\| = \max_i \sum_{j=1}^k |a_{ij}|$. (Throughout this appendix, $\lim_n$ denotes the limit for $n \to \infty$.) Since the sequence $\|A^n\|^{1/n}$ is monotone decreasing, $r \leq \|A^n\|^{1/n}$ holds for every $n \geq 1$. Nonnegative matrices have the following important property:

Theorem A.9. *Let* $A \geq 0$. *Then the spectral radius* r *of* A *is an eigenvalue and there is at least one nonnegative eigenvector* $\boldsymbol{x} \geq 0$ ($\boldsymbol{x} \neq \boldsymbol{0}$), *i.e.,* $A\boldsymbol{x} = r\boldsymbol{x}$. *In addition, if* A *has an eigenvalue* λ *with an associated positive eigenvector, then* $\lambda = r$.

We use the notation $A^n = (a_{ij}^{(n)})$ for nth powers. A nonnegative matrix A is called *irreducible* if for every pair of indices (i, j) an integer $n = n(i, j) \geq 1$ exists such that $a_{ij}^{(n)} > 0$. Now we state the *Theorem of Perron–Frobenius*.

Theorem A.10. *If* A *is irreducible, then the following hold:*

1. *The spectral radius r is positive and a simple root of the characteristic equation.*

2. *To r there corresponds a positive right eigenvector $\boldsymbol{x} > 0$ such that $\mathsf{A}\boldsymbol{x} = r\boldsymbol{x}$, and $\boldsymbol{x}$ is unique except for multiplication by a positive constant.*

3. *No other eigenvalue of A is associated with a nonnegative eigenvector.*

This theorem is sufficient to prove our existence, uniqueness, and stability results for the haploid mutation-selection model in continuous time. In discrete time a stronger condition than irreducibility is needed.

A nonnegative matrix A is called *primitive* if an integer $n \geq 1$ exists such that $\mathsf{A}^n > 0$. Obviously, every positive matrix is primitive, and every primitive matrix is irreducible.

Theorem A.11. *For an irreducible matrix A with spectral radius r, the following assertions are equivalent:*

1. *A is primitive.*

2. *$|\lambda| < r$ for all eigenvalues $\lambda \neq r$ of A.*

3. *$\lim_n (r^{-1}\mathsf{A})^n$ exists.*

Concerning property 3, it is readily shown that for an arbitrary matrix A, $\lim_n \mathsf{A}^n = 0$ is equivalent to $r(\mathsf{A}) < 1$, and that $r(\mathsf{A}) > 1$ always implies that $\lim_n \mathsf{A}^n$ does not exist. If $r(\mathsf{A}) = 1$, then $\lim_n \mathsf{A}^n$ exists if and only if $r(\mathsf{A}) = 1$ is a simple root of the minimal polynomial and all other eigenvalues satisfy $|\lambda| < 1$.

A stronger and more precise statement of Theorem B.3.3. is the following:

Theorem A.12. *Let A be primitive with spectral radius r and corresponding eigenvector $\boldsymbol{x} > 0$. Then there exists a decomposition $\mathsf{A} = r\mathsf{P} + \mathsf{B}$, where P is a projection on the eigenspace spanned by $\boldsymbol{x}$ (i.e., for every $\boldsymbol{y} \in \mathbb{R}^k$ there is a constant c such that $\mathsf{P}\boldsymbol{y} = c\boldsymbol{x}$, and $\mathsf{P}\boldsymbol{x} = \boldsymbol{x}$), $\mathsf{PB} = \mathsf{BP} = 0$, and $r(\mathsf{B}) < 1$. Consequently,*

$$\lim_n (r^{-1}\mathsf{A})^n \boldsymbol{y} = c\boldsymbol{x} + \lim_n (r^{-1}\mathsf{B})^n \boldsymbol{y} = c\boldsymbol{x} \tag{A.12}$$

holds for all $\boldsymbol{y} \in \mathbb{R}^k$.

Finally, the exponential

$$e^{\mathsf{A}} = \sum_{n=0}^{\infty} \frac{1}{n!} \mathsf{A}^n \tag{A.13}$$

of an irreducible matrix A is always positive and, hence, primitive. It follows that

$$\lim_{t \to \infty} e^{-rt} e^{\mathsf{A}t} \boldsymbol{y} = c\boldsymbol{x} \tag{A.14}$$

for some constant c depending on $\boldsymbol{y}$.

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