Some Mathematical Models in Evolutionary Genetics

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1. Introduction

As explained beautifully in Warren Ewens' chapter, mathematical models played a decisive role in reconciling Mendelian genetics with Darwin's theory of evolution by natural selection. Out of this successful enterprise during the early 20th century, the field of population genetics emerged. Population genetics is concerned with the study of the genetic composition of populations. This composition may be changed by segregation, selection, mutation, recombination, mating, migration, and other genetic, ecological, and evolutionary mechanisms. Population genetics is the field in which these mechanisms, their interactions, and their evolutionary consequences are investigated. Because Darwinian evolution is impossible without selection and inheritance, population genetics forms the main corner stone of evolutionary theory. The founding fathers of population genetics were R.A. Fisher, S. Wright, and J.B.S. Haldane. They not only developed almost all the basic theory and employed it to empirical findings and data, but they also initiated numerous experiments to test their theories. Much of their work was highly mathematical, far beyond what the majority of their fellow geneticists and biologists could understand. Almost as a by-product, their work laid the foundations for modern statistics and for important developments in stochastic processes.

One of the first crucial insights, an immediate consequence of the Hardy-Weinberg law, was that Mendelian inheritance preserves genetic variation on which natural selection can act. Early work culminated in Fisher's (1930) Fundamental Theorem of Natural Selection (FTNS) which he formulated as

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

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Although it was argued convincingly that this statement has been misinterpreted for many decades (see Ewens' chapter), the 'classical' interpretation has led to deep insights into the evolutionary process. Fisher's Fundamental Theorem not only implies that evolution is impossible in the absence of genetic variation, but it gave rise to important quantitative predictions about the response to selection. It is the purpose of this chapter to present some of the most fundamental results about the evolutionary dynamics of a population subject to selection.

I shall first treat the classical case when selection acts on a single diploid locus at which an arbitrary number of alleles can occur. Then I turn to generalizations that include recombination and selection at multiple loci, and point out extensions that include migration or frequency-dependent selection. Eventually, the selection response and the evolution of (multivariate) quantitative traits is studied. In this case, the theory is formulated in terms of directly measurable quantities and thus is relatively easily amenable to experimental and empirical testing. Special cases of this theory have been successfully employed for many decades in animal and plant breeding.

Throughout this chapter, we treat deterministic models, i.e., systems of difference or differential equations. Hence, we assume that populations are effectively infinite, so that stochasticity can be ignored. Of course, it has been known since the early days that reproduction and selection have inherent stochastic effects. Incorporation of these effects, in particular of random genetic drift, produces models that are formulated in terms of (usually Markovian) stochastic processes and adds considerable mathematical complexity. The study of such models has been an active research area since it was initiated by Fisher and Wright, which nowadays, especially in the context of the inference of past evolutionary events from molecular data, seems more relevant than ever. Keeping in mind the most important effects of random genetic drift (the reduction of genetic variance by an approximate factor of $1 - 1/(2N)$ per generation and the eventual fixation or loss of alleles), deterministic models are valuable guides to understanding the consequences of the interaction of two or more evolutionary mechanisms that would not be amenable to analysis otherwise. They also yield close approximations for short-term or medium-term predictions of evolutionary change.

2. A single locus

In general, I prefer to formulate models for populations with discrete, nonoverlapping generations because this allows their derivation from a well-defined life cycle based on biological principles. Continuous-time models are sometimes closer to biological reality and frequently easier to treat mathematically. However, their derivation often involves mathematically inconsistent assumptions (see below).

Throughout, we assume that organisms are diploid, that the genotype frequencies are the same in both sexes, that adults mate at random with

respect to considered gene loci, and that selection acts on juveniles through differential viabilities that are constant. As a consequence of random mating, zygotes are in Hardy-Weinberg proportions, and it is sufficient to consider gamete frequencies (instead of genotype frequencies) among zygotes. For a detailed treatment including proofs and more complete references, we refer to Bürger (2000, Chaps. I.9 and I.10).

2.1. Discrete, non-overlapping generations

Suppose that at a given gene locus the I alleles $A_1, \dots, A_I$ occur. We denote the frequency of allele A_i by p_i and the fitness of genotype A_iA_j by $w_{ij} = w_{ji} \geq 0$. Then the (marginal) fitness of allele A_i and the mean fitness of the population are

$$w_i = \sum_j w_{ij} p_j \quad \text{and} \quad \bar{w} = \sum_i w_i p_i = \sum_{i,j} w_{ij} p_i p_j \,, \tag{2.1}$$

respectively. The frequency p_i' of allele A_i in the next generation is given by

$$p_i' = p_i \frac{w_i}{\bar{w}} \quad \text{for } i = 1, \dots, I \,. \tag{2.2}$$

This recursion preserves the relation $\sum_i p_i = 1$[1] and describes the evolution of allele frequencies at a single autosomal locus in a diploid population. It describes a discrete dynamical system on the simplex

$$\mathsf{S}_I = \left\{ p = (p_1, \dots, p_I)^T \in \mathbb{R}^I : \sum_i p_i = 1,\, p_i \geq 0,\, i = 1, \dots, I \right\} . \tag{2.3}$$

For multiplicative fitnesses, i.e., if constants v_i exist such that $w_{ij} = v_i v_j$ for every i and j, (2.2) reduces to the selection dynamics of a haploid species. It has the same structure as (2.2) but the linear term w_i is replaced by the constant v_i, and $\bar{w}$ by $\bar{v}$.

The equilibria of (2.2) are the solutions of the system

$$p_i(w_i - \bar{w}) = 0 \,, \quad i = 1, \dots, I \,. \tag{2.4}$$

Obviously, the monomorphic states ($p_i = 1$ for some allele A_i) are always equilibria. If equilibria are isolated, then at most $2^I - 1$ equilibria exist. If an internal equilibrium (i.e., $p_i > 0$ for every i) exists, it is uniquely determined. If an internal equilibrium is (asymptotically) stable, then the (asymptotic) stability is global. This follows from (2.5) below because $\bar{w}$ is concave then.

The selection dynamics (2.2) has the important property that mean fitness is nondecreasing along trajectories. More precisely, it has been shown that

$$\Delta\bar{w} \geq 0 \quad \text{and} \quad \Delta\bar{w} = 0 \quad \text{only at equilibria} \tag{2.5}$$

(Scheuer and Mandel 1959, Mulholland and Smith 1959), where $\Delta\bar{w} = \bar{w}' - \bar{w}$. A particularly elegant proof is due to Kingman (1961). Fisher not only stated

[1] Throughout, sums or products without ranges indicate summation over all admissible indices, e.g., $\sum_i = \sum_{i=1}^I$.

that mean fitness is nondecreasing but that its rate of change is equal to the additive genetic variance in fitness,

$$\sigma_A^2 = 2\sum_i p_i(w_i - \bar{w})^2 \,. \tag{2.6}$$

In general, σ_A^2 is strictly smaller than the total genetic variance $\sigma_G^2 = \sum_{i,j} p_i p_j (w_{ij} - \bar{w})^2$, and $\sigma_A^2 = \sigma_G^2$ if there is no dominance.

The classical interpretation of the FTNS has been that

$$\Delta\bar{w} = \sigma_A^2/\bar{w} \,, \tag{2.7}$$

at least approximately. Unless there is no dominance, (2.7) does generally not hold exactly. Importantly, error estimates of the degree of failure of the classical interpretation of the FTNS have been derived. Let

$$s = (\max_{i,j} w_{ij} - \min_{i,j} w_{ij})/\min_{i,j} w_{ij} \tag{2.8}$$

denote the biggest selection coefficient. It measures the maximum strength of selection and, hence, the maximum response to selection,

$$\max_i \frac{|\Delta p_i|}{p_i} \le s \,, \tag{2.9}$$

where Δp_i is the change in gene frequency across one generation (which, as a consequence of the Hardy-Weinberg law, equals the change caused by selection).

Nagylaki (1991) proved

$$\Delta\bar{w} = \frac{\sigma_A^2}{\bar{w}}(1 + E) \,, \tag{2.10}$$

where

$$|E| \le \tfrac{1}{2} s \,, \tag{2.11}$$

and $E = 0$ in the absence of dominance. In particular, for weak selection ($s \ll 1$), the following asymptotic version of the FTNS is valid:

$$\Delta\bar{w} = \frac{\sigma_A^2}{\bar{w}} + O(s^3) \,. \tag{2.12}$$

If, in addition and without loss of generality, $\max_{i,j} w_{ij}$ is normalized to 1, then $\bar{w} \approx 1$ and $\Delta\bar{w} \approx \sigma_A^2$. Because typical selection coefficients among segregating alleles rarely exceed 10%, and often are much smaller, $\Delta\bar{w} \approx \sigma_A^2$ can be expected to provide a good approximation to reality if viability selection acts on a single locus.

Before we turn to generalizations and limitations, we briefly treat the continuous-time model for which some nice and important mathematical properties can be derived with great ease. In particular, we present alternative representations of the allele-frequency dynamics that provide deeper insight into the evolutionary dynamics and also in they way how the selection response depends on the variational properties of a population.

2.2. Continuous time

The preferable way to derive the continuous-time version of the selection dynamics (2.2) is to rescale fitnesses and time according to

$$w_{ij} = 1 + \epsilon m_{ij} \quad \text{and} \quad t = \lfloor \tau/\epsilon \rfloor \,, \tag{2.13}$$

where m_{ij} is called the Malthusian fitness (or parameter) of A_iA_j and ϵ can be interpreted as the selection intensity or the generation time. Let $m_i = \sum_j m_{ij}p_j$ and $\bar{m} = \sum_{i,j} m_{ij}p_ip_j$ denote the marginal fitness of allele A_i and the mean fitness of the population, respectively. Then, setting $q_i = q_i(\tau) = p_i(t)$, (2.2) is rearranged such that the limit of $(q_i(\tau+\epsilon) - q_i(\tau))/\epsilon$ as $\epsilon \to 0$ can be computed. Returning to the notation p_i and t instead of q_i and τ, one obtains the weak-selection approximation

$$\dot{p}_i = p_i(m_i - \bar{m}) \,, \quad i = 1, \ldots, I \,. \tag{2.14}$$

This is a dynamical system on the simplex S_I which has the same equilibria as the corresponding discrete-time system.

A proper derivation of (2.14) from biological principles requires the inclusion of age structure. However, when birth and selection occur continuously, Hardy-Weinberg proportions no longer hold and the model needs to be formulated in terms of genotype frequencies. Equation (2.14) is obtained only if a stable age distribution is assumed and Hardy-Weinberg proportions are (inconsistently) imposed (see Nagylaki and Crow 1974 for a lucid treatment).

For the dynamics (2.14), a one-line calculation shows that

$$\dot{\bar{m}} = \sigma_A^2 \,, \tag{2.15}$$

where $\sigma_A^2 = 2\sum_i p_i(m_i - \bar{m})$ is the additive genetic variance in Malthusian fitness. According to the classical view, this has been the quintessence of the FTNS.

The selection dynamics (2.14) can be represented in other ways which provide interesting perspectives and insights. To this aim, we define the indicator variable

$$f_i(A_kA_l) = \begin{cases} 1 & \text{if } k = l = i \,, \\ \frac{1}{2} & \text{if } k \neq l \text{ and } k = i \text{ or } l = i \,, \\ 0 & \text{otherwise} \,, \end{cases} \tag{2.16}$$

where i is fixed and k and l are independent and have probability distribution p. Thus, f_i measures the frequency of allele A_i in a given genotype. It has expectation p_i. The associated $I \times I$ covariance matrix is designated $\mathbf{G}_p = (g^{ij})$, where

$$g^{ij} = \mathrm{Cov}(f_i, f_j) = \tfrac{1}{2}p_i(\delta_{ij} - p_j) \,, \tag{2.17}$$

and δ_{ij} is the Kronecker delta.

Then the allele-frequency dynamics (2.14) can be written as a generalized gradient system on S_I (Svirezhev 1972, Shahshahani 1979),

$$\dot{p} = \mathbf{G}_p \, \nabla\bar{m} = \mathbf{G}_p \left(\frac{\partial\bar{m}}{\partial p_1}, \ldots, \frac{\partial\bar{m}}{\partial p_n} \right)^T \,. \tag{2.18}$$

Hence, with respect to the associated metric, $\dot{p}$ is perpendicular to the level surfaces of $\overline{m}$. We also point out that the matrix $\mathbf{G}_p$ plays a central role in the diffusion approximation of the multiallelic Wright-Fisher model. There, it occurs not only in the drift coefficients but also as the matrix of diffusion coefficients in the generator. As a consequence, the stationary distribution can be determined explicitly for general selection and a certain class of mutation matrices (Bürger 2000, Appendix E).

For a diallelic locus, the single frequency $p = p_1$ is sufficient to describe the state of the system. Then (2.18) simplifies to Wright's (1935) result

$$\dot{p} = \frac{p(1-p)}{2} \frac{\mathrm{d}\overline{m}}{\mathrm{d}p} \,. \tag{2.19}$$

Finally, if we define the indicator variable $m(A_k A_l) = m_{kl}$, a simple calculation establishes the covariance formulation (Li 1967)

$$\dot{p}_i = \mathrm{Cov}(f_i, m) \tag{2.20}$$

which, in fact, holds under much more general circumstances (Price 1970, Lessard 1997). Both representations, (2.18) and (2.20) have important analogs in quantitative genetics that will be treated below.

2.3. Limitations

If additional evolutionary forces are allowed to act, then mean fitness does often not increase, not even in the continuous-time approximation. For instance, if mutation is included, then already with three alleles stable limit cycles can exist (Hofbauer 1985, Baake and Wiehe 1997). The examples require that mutation rates and selection coefficients are of similar magnitude. For a detailed and very general treatment of mutation-selection models, including a continuum of possible alleles, see Bürger (2000, Chaps. 3, 4, 6). Under frequency-dependent selection, mean fitness may be decreasing along all trajectories (Wright 1948; see Schneider 2008, 2010 for a detailed investigation). Further, non-random mating, fertility selection, and migration may lead to a decrease of mean fitness and to complex dynamics. We study multiple loci and recombination in more detail below.

3. Multiple loci

For two recombining loci under selection, the existence of stable limit cycles has been established for continuous-time (Akin 1979, 1982) and discrete-time models (Hastings 1981b, Hofbauer and Iooss 1984). Therefore, in general, mean fitness does not increase. Essentially, the demonstration of limit cycles requires that selection coefficients and recombination rates are of similar magnitude and that fitnesses of loci interact non-additively, i.e., there is epistasis. However, for weak selection as well as for weak epistasis, we shall see that the evolutionary dynamics is simple and extensions of the single-locus results on the increase of mean fitness are available.

There are several reasons why the complexity of multilocus models exceeds that of single-locus models by far. First, it is not sufficient to use the allele frequencies at the different loci. Instead, the evolutionary dynamics needs to be formulated in terms of gamete frequencies. This is so because selection generates nonrandom associations, called linkage disequilibria, among the alleles at different loci. Recombination breaks up these associations to a certain extent but changes gamete frequencies in a quite complex way. If all gamete frequencies are the products of the frequencies of the constituent alleles, then the population is said to be in linkage equilibrium. If this is the case, then the dynamics is simplified greatly and no complex behavior can occur. For reasons of continuity, one also expects simple dynamical behavior in quasi-linkage equilibrium, i.e., close to linkage equilibrium. These considerations can be made precise in a way outlined below. First, however, we need to introduce the multilocus selection model. Essentially, our formulation follows Nagylaki (1993) and Nagylaki et al. (1999).

3.1. The multilocus selection model

As before, we consider a diploid, randomly mating population with discrete, non-overlapping generations, in which the two sexes need not be distinguished. Selection acts through differential viabilities on juveniles, which are time and frequency independent (although this can be relaxed to a certain extent). The linkage map is arbitrary but mutation and random genetic drift are ignored.

The genetic system consists of $L \geq 1$ loci. At locus n there are $I_n \geq 2$ alleles, $A_{i_n}^{(n)}$ $(i_n = 1, \ldots, I_n)$. We use the multi-index $i = (i_1, \ldots, i_L)$ as an abbreviation for the gamete $A_{i_1}^{(1)} \ldots A_{i_L}^{(L)}$ and write $I = \prod_n I_n$ for the number of gametes. We use the letters i, j, l for gametes and k, n for loci.

Let $p_i = p_i(t)$ represent the frequency of gamete i among zygotes in generation t, and $p = (p_1, \ldots, p_I)^T$ the vector of all gamete frequencies. The frequency of allele $A_{i_n}^{(n)}$ among gametes is

$$p_{i_n}^{(n)} = \sum_{i|i_n} p_i \,, \tag{3.1}$$

where the sum runs over all multi-indices i with the nth component fixed as i_n. Let w_{ij} denote the fitness of genotype ij. We designate the marginal fitness of gamete i and the mean fitness of the population by

$$w_i = w_i(p) = \sum_j w_{ij} p_j \quad \text{and} \quad \bar{w} = \bar{w}(p) = \sum_{i,j} w_{ij} p_i p_j \,, \tag{3.2}$$

respectively.

After selection the frequency of the genotype ij is $p_i p_j w_{ij}/\bar{w}$. The frequency of gamete i in the next generation, i.e., after recombination and reproduction, is

$$p_i' = \sum_{j,l} R_{i,jl} p_j p_l w_{jl}/\bar{w} \,, \tag{3.3}$$

where $R_{i,jl}$ is the probability that during gametogenesis the paternal haplotypes j and l produce a gamete i by recombination.

The complications introduced by recombination are disguised by the terms $R_{i,jl}$ which depend on the recombination frequencies among all subsets of loci. To obtain an analytically useful representation of the dynamics (3.3), more effort is required.

Let $\{\mathsf{K},\mathsf{N}\}$ be a nontrivial decomposition of the set L of all loci, i.e., K and its complement $\mathsf{N} = \mathsf{L} \setminus \mathsf{K}$ are each proper subsets of L and contain at least one locus. (The decompositions $\{\mathsf{K},\mathsf{N}\}$ and $\{\mathsf{N},\mathsf{K}\}$ are identified.) We designate by c_{K} the probability of reassociation of the genes at the loci in K, inherited from one parent, with the genes at the loci in N, inherited from the other.

We designate the recombination frequency between loci k and n, where $k < n$, by c_{kn}. It is given by

$$c_{kn} = \sum_{\mathsf{K}\in\mathsf{L}_{kn}} c_{\mathsf{K}}\,, \tag{3.4}$$

where $\mathsf{L}_{kn} = \{\mathsf{K} \subset \mathsf{L} : k \in \mathsf{K} \text{ and } n \in \mathsf{N}\}$. We assume that all pairwise recombination rates c_{kn} are positive. Hence,

$$c_{\min} = \min_{k,n:k<n} c_{kn} > 0\,. \tag{3.5}$$

We define

$$D_i = \frac{1}{\bar{w}} \sum_j \sum_{\mathsf{K}} c_{\mathsf{K}} \left(w_{ij}\, p_i p_j - w_{i_{\mathsf{K}} j_{\mathsf{N}}, j_{\mathsf{K}} i_{\mathsf{N}}}\, p_{i_{\mathsf{K}} j_{\mathsf{N}}}\, p_{j_{\mathsf{K}} i_{\mathsf{N}}}\right)\,, \tag{3.6}$$

where $\sum_{\mathsf{K}}$ runs over all (different) decompositions $\{\mathsf{K},\mathsf{N}\}$ of L, and $i_{\mathsf{K}} j_{\mathsf{N}}$ is the gamete consisting of alleles $A_{i_k}^{(k)}$ and $A_{j_n}^{(n)}$ for loci in K and N, respectively. D_i is a measure of linkage disequilibrium in gamete i. Then the recursion equations describing the evolution of gamete frequencies are given by (Nagylaki 1993; Bürger 2000, p. 56):

$$p_i' = p_i \frac{w_i}{\bar{w}} - D_i\,. \tag{3.7}$$

Obviously, this is a much more complicated dynamical system (on S_I) than the single-locus selection dynamics (2.2).

Let

$$\Lambda_0 = \left\{p : p_i = p_{i_1}^{(1)} \cdot \ldots \cdot p_{i_L}^{(L)}\right\} \subseteq \mathsf{S}_I \tag{3.8}$$

denote the *linkage-equilibrium manifold* (also called the Wright manifold). If there is no position effect, i.e., if $w_{ij} = w_{i_{\mathsf{K}} j_{\mathsf{N}}, j_{\mathsf{K}} i_{\mathsf{N}}}$ for every i, j, and K, then $D_i = 0$ for every $p \in \Lambda_0$. Hence,

$$\Lambda_0 \subseteq \{p : D = 0\}\,, \tag{3.9}$$

where $D = (D_1, \ldots, D_I)^T$ is the vector of all linkage disequilibria. In the absence of selection equality holds in (3.9).

3.2. The additive genetic variance

Below, and in evolutionary genetics in general, the so-called additive genetic variance, σ_A^2, plays a central role. Its definition is complicated because it is based on the concept of the additive (or average) effect $\alpha_{i_n}^{(n)}$ of an allele $A_{i_n}^{(n)}$. In words, the additive effects provide the best linear approximation to the deviations of the fitnesses from mean fitness. More precisely, the $\alpha_{i_n}^{(n)}$ are obtained by minimizing the quantities

$$(w_{ij} - \bar{w}) - (\alpha_i + \alpha_j)\,, \tag{3.10}$$

where

$$\alpha_i = \sum_n \sum_{i_n} \alpha_{i_n}^{(n)}\,, \tag{3.11}$$

in the sense of a least-squares approximation. If all genotype frequencies are positive, the vector $(\alpha_{i_n}^{(n)})$ is obtained as the unique solution of an $I \times I$-dimensional linear system (e.g., Bürger 2000, Chap. II.3).

It is important to note that, in general, the additive effects are not constant but depend on the frequency distribution p. In the present case, where we assume Hardy-Weinberg proportions, they depend only on the allele frequencies and the pairwise linkage disequilibria. Essentially, this procedure was introduced by Fisher (1918) and is the basis of an analysis of variance (see also Ewens' chapter).

Given the additive effects and assuming Hardy-Weinberg proportions, the additive genetic variance is defined as

$$\sigma_A^2 = 2\sum_i p_i \alpha_i^2\,. \tag{3.12}$$

The additive genetic variance may evolve as a consequence of changes in allele frequencies or additive effects (see Section 4.4). The latter may change as a consequence of changes in the (pairwise) linkage disequilibria, even if allele frequencies remain constant. In the absence of epistasis and of dominance, the additive effects are constant and σ_A^2 is equal to the total genetic variance.

In general, the total genetic variance can be written as the sum of the additive genetic variance and the residual variance. The latter can be decomposed further into variance components arising from nonadditive effects within loci (dominance), nonadditive effects between loci (epistasis), and all kinds of interactions. For detailed and much more general treatments we refer to Bürger (2000, Chap. II.3) and especially to Bulmer (1980, Chap. 6) and Nagylaki (1993).

3.3. Weak epistasis

Weak epistasis means that the fitness scheme has the form

$$w_{ij} = \sum_n u_{i_n j_n}^{(n)} + \epsilon e_{ij}\,, \tag{3.13}$$

where ϵ, the strength of epistasis, is sufficiently small and $|e_{ij}| \leq 1$. We assume $u_{i_n j_n}^{(n)} > 0$.

If $\epsilon = 0$, then there is no (additive) epistasis. We review this case first. Let s be defined as in (2.8), where now ij is a multilocus genotype. Thus, s is the biggest multilocus selection coefficient. We call a point $p \in \mathsf{S}_I$ a selection equilibrium if it satisfies $p_i(w_i - \bar{w}) = 0$ for every i. The set of all points which are a selection equilibrium for $\epsilon = 0$ is denoted by F.

We summarize the main results that hold for (3.7) if epistasis is absent.

Theorem 3.1. (a) *Mean fitness is nondecreasing, $\bar{w}' \geq \bar{w}$ (Ewens 1969), and $\bar{w}' = \bar{w}$ holds exactly on the set F of selection equilibria (Nagylaki et al. 1999).*

(b) $\Delta\bar{w} = \sigma_A^2/\bar{w} + O(s^3)$ *as* $s \to 0$ *(Nagylaki 1989).*

(c) $\Delta\bar{w} = \dfrac{\sigma_A^2}{\bar{w}}(1 + E)$, *where* $|E| \leq \frac{1}{2}s$, *and* $E = 0$ *if dominance is absent (Nagylaki 1991).*

(d) *Every trajectory of* (3.7) *converges to an equilibrium point (Kun and Lyubich 1980).*

(e) *A point p is an equilibrium of* (3.7) *if and only if it is both a selection equilibrium for each locus (with fitnesses given by the $u_{i_n j_n}^{(n)}$) and it is in linkage equilibrium (Lyubich 1992, Nagylaki et al. 1999).*

We point out that (c) implies that mean fitness remains constant if there is no additive genetic variation. Nevertheless, gamete frequencies may change due to linkage disequilibrium.

If fitnesses are multiplicative instead of additive, then mean fitness may decrease and (with two diallelic loci) two asymptotically stable equilibria in linkage disequilibrium, one with $D > 0$ the other with $D < 0$, may coexist (Karlin and Feldman 1978, Hastings 1981a). In particular, the linkage-equilibrium manifold Λ_0 is in general not attracting. However, in contrast to the case of additive fitnesses, Λ_0 is forward invariant. For a review, see Bürger (2000, Chap. II.1).

The next theorem summarizes the results that can be extended to weak epistasis.

Theorem 3.2 (Nagylaki et al. 1999). *If, for $\epsilon = 0$, every equilibrium is hyperbolic, as is generic, then for sufficiently small ϵ the following hold:*

(a) *Every equilibrium is within $O(\epsilon)$ of the corresponding equilibrium (on $D = 0$) with $\epsilon = 0$ and has the same stability properties. Unstable boundary equilibria may leave the state space if perturbed.*

(b) *Every trajectory converges to an equilibrium point.*

(c) *If p is bounded away from the set F, then $\Delta\bar{w} > 0$.*

The mathematical essence of this result is that it is a global perturbation result that not only establishes local stability properties of a perturbed equilibrium but proves that the perturbed dynamics is qualitatively the same as the much simpler dynamics with $\epsilon = 0$. If $\epsilon > 0$, it is no longer true that mean fitness is nondecreasing. Nagylaki et al. (1999) gave an example in which for every $\epsilon > 0$, $\Delta\bar{w} \leq 0$ holds near and at the set F, and equality holds only at

equilibrium. However, mean fitness increases until evolution has nearly come to a halt, which occurs when a neighborhood of F has been reached.

General results such as those above are biologically relevant because epistasis is wide spread, and sign and magnitude can vary widely. They provide the mathematical justification to investigate specific models by perturbation methods.

3.4. Weak selection

To study weak selection, we assume

$$w_{ij} = 1 + s\omega_{ij}\,, \tag{3.14}$$

where the selection intensity s is a nonnegative, sufficiently small parameter, and the selection coefficients satisfy $|\omega_{ij}| \le 1$. We speak of weak selection (or loose linkage) if s is small relative to the minimum two-locus recombination rate $c_{\min}$ (3.5).

In the absence of selection ($s = 0$), the dynamics (3.7) is degenerate because every point $p \in \Lambda_0$ is an equilibrium. In addition, Λ_0 is invariant and globally attracting at a geometric rate (Lyubich 1971, Nagylaki 1993). For generic conditions, the rate of approach is $1 - c_{\min}$.

For weak selection, the theory of normally hyperbolic manifolds implies the existence of a smooth invariant manifold Λ_s close to Λ_0, which is globally attracting at a geometric rate for (3.7). The manifold Λ_s is characterized by an equation of the form $D = s\zeta(\rho, s)$, where ζ is a smooth function of the vector ρ of all gene frequencies. Thus, on Λ_s, and more generally, for any initial values, after a long time, $D(t) = O(s)$. It follows that on Λ_s, linkage disequilibria are of order s and, in fact, change very slowly, i.e., $\Delta D(t) = O(s^2)$. Therefore, Λ_s is called the quasi-linkage equilibrium manifold (Nagylaki et al. 1999).

Let us define the gametic, allelic, and average selection coefficients at linkage equilibrium by

$$\omega_i = \sum_j \omega_{ij} \prod_n p_{i_n}^{(n)}\,, \quad \omega_{i_n}^{(n)} = \sum_{i|i_n} \omega_i \prod_{k:k\neq n} p_{i_k}^{(k)}\,, \quad \bar\omega = \sum_i \omega_i \prod_n p_{i_n}^{(n)}\,, \tag{3.15}$$

respectively. Then the dynamics in the neighborhood of Λ_s can be shown to be a perturbation of the so-called *weak-selection limit*,

$$\dot p_{i_n}^{(n)} = p_{i_n}^{(n)}(\omega_{i_n}^{(n)} - \bar\omega)\,, \tag{3.16}$$

which 'lives' on $\mathsf{S}_{I_1} \times \cdots \times \mathsf{S}_{I_L}$, the natural parameterization of the linkage-equilibrium manifold Λ_0.

The main results can be summarized as follows:

Theorem 3.3 (Nagylaki 1993; Nagylaki et al. 1999). *Suppose that, as is generic, all equilibria of* (3.16) *are hyperbolic and s is sufficiently small.*

(a) *The set of equilibria of* (3.7) *contains only isolated points and every equilibrium is within an $O(s)$ neighborhood of the corresponding equilibrium of* (3.16) *on* Λ_0.

(b) *There is a one-to-one correspondence between these equilibria. Every pair has the same stability properties.*
(c) *Every trajectory of the multilocus dynamics* (3.7) *converges to an equilibrium point.*
(d) *The so-called Asymptotic Fundamental Theorem of Natural Selection holds: If* $t \geq t_2$, *then*

$$\Delta\bar{w} = \frac{\sigma_A^2}{\bar{w}} + O(s^3) \quad as \quad s \to 0\,, \tag{3.17}$$

where $t \geq t_2 \sim 2\ln s/\ln(1 - c_{min})$.
(e) *If* $t \geq t_2$ *and* p *is bounded away from the set of equilibria, then* $\Delta\bar{w}(p) > 0$.

These results have several important consequences. (i) They show that no complex dynamical behavior can occur. (ii) Under weak selection the equilibrium and stability structure can be inferred from the much simpler weak-selection limit (3.16). The latter is not only a generalized gradient system, analogous to (2.18), but its dimension is (much) lower than that of the full dynamics. If greater accuracy than provided by the weak-selection limit is needed, quasi-linkage equilibrium approximations can sometimes be developed (e.g., Turelli and Barton 1990). (iii) The mean fitness may decrease during the short period, of order $\ln(1/s)$ generations, of approach to Λ_s. Because this initial period is short, relatively little change in allele frequencies occurs during it. After a long time, $\bar{w}$ may also decrease close to equilibrium. For intermediate times, $\bar{w}$ increases. This is during the period when most of the (evolutionary important) gene frequency-change occurs.

Finally, let us assume that both selection and recombination are weak, i.e., for small $\epsilon \geq 0$ and constants m_{ij} and r_{K}, we posit

$$w_{ij} = 1 + \epsilon m_{ij} \quad \text{and} \quad c_{\mathsf{K}} = \epsilon r_{\mathsf{K}} \tag{3.18}$$

for all gametes i, j and subsets $\mathsf{K} \subseteq \mathsf{L}$. Then, proceeding similarly as in Section 2.2, the continuous-time dynamics

$$\dot{p}_i = p_i(m_i - \bar{m}) - \sum_{\mathsf{K}} r_{\mathsf{K}}\big[p_i - p_{i_{\mathsf{K}}}^{(\mathsf{K})} p_{i_{\mathsf{N}}}^{(\mathsf{N})}\big] \tag{3.19}$$

is derived, where $p_{i_{\mathsf{K}}}^{(\mathsf{K})}$ designates the marginal frequency of the gamete with components i_k for the loci $k \in \mathsf{K}$ fixed. Results 3.2 and 3.3 also hold for (3.19).

3.5. Generalizations

Without giving much detail, we mention that some of the above results can be generalized to models that include migration among subpopulations or frequency-dependent selection in a panmictic population.

If epistasis and migration are weak, then statements (a) and (b) of Theorem 3.2 remain valid (Theorem 5.4 in Bürger 2009a). If selection is weak relative to migration and recombination, then statements (a), (b), (c), and (e) of Theorem 3.3 hold subject to the following modifications (Bürger 2009a,

Theorems 4.3 and 4.8): Λ_0 is replaced by the manifold on which linkage equilibrium holds and gamete frequencies are spatially homogeneous. The weak-selection limit describes the change of spatially averaged allele frequencies. The single-locus case was treated by Nagylaki and Lou (2007).

For a multilocus model, in which frequency-dependent selection is caused by intraspecific competition for a continuum of resources, a weak-selection limit was derived and analyzed by Bürger (2005). It was further developed by Schneider (2006, 2007), who applied it to study long-term evolution under disruptive frequency-dependent selection. Not surprisingly, the conclusions drawn on the basis of a proper population-genetic analysis partially differ from those derived from an adaptive dynamics approach which, as is usual in ecological modeling, ignores intraspecific variation.

4. Quantitative traits

Quantitative traits are characters that vary (almost) continuously and can be measured on a metric scale. Typical examples include body weight or height, abdominal bristle number in *Drosophila*, milk yield, oil content in maize, and, more generally, many morphological, physiological, or economically important traits. Also fitness can be considered as a quantitative trait. Quantitative traits have genetic and environmental components. They have a complex genetic basis in the sense that they are determined by many genes, most of which have small effects although some may have very large effects. In addition, epistasis, pleiotropy (which means that one gene affects more than one trait), and genotype-environment interaction are common (e.g., Bürger 2000, Mackay 2001, Barton and Keightley 2002). An important feature is that, on an appropriate scale, quantitative traits are often normally distributed. In view of their multifactorial determination and the Central Limit Theorem this is not too surprising.

In the models treated below we assume that there is no genotype-environment interaction and that the environmental contribution E can be treated as white noise, i.e., as a Gaussian random variable with mean zero. Thus, we can write the phenotypic value P as

$$P = G + E\,, \tag{4.1}$$

where the genetic and environmental components, G and E, are independent. Unless stipulated otherwise, we assume that G is determined additively, i.e., trait effects can be assigned directly to alleles and G is the sum of the effects of the paternal and maternal alleles of an individual at the contributing loci. Then all genetic variance is additive (Section 3.2) and the phenotypic variance can be written as

$$\sigma_P^2 = \sigma_A^2 + \sigma_E^2\,. \tag{4.2}$$

In general, the phenotypic variance can be decomposed into a genetic, an environmental, and an interaction component. As indicated in Section 3.2,

the genetic variance can be decomposed further into additive, dominance, epistatic, and various interaction components.

Of fundamental importance in quantitative genetics is the (narrow sense) heritability, h^2. It is defined as the ratio of additive genetic to total phenotypic variance:

$$h^2 = \sigma_A^2/\sigma_P^2\,. \tag{4.3}$$

The heritability can be estimated from correlations among relatives (Bulmer 1980). Most traits, in most populations, show substantial heritabilities (typically between 20% and 50%), and a few patterns have been identified (see e.g. Barton and Keightley 2002). Thus, much trait variation is inherited, in fact more than can be explained by simple universal mechanisms (see below).

What distinguishes quantitative-genetic models from many other models in biology is that they are formulated in terms of quantities that are measurable (and not only in the lab or in breeding programs but also, with greater effort, in nature). The basis for this theory was laid by Fisher and Wright. Over the decades the additive model has received widespread empirical support in the sense that cases where the additive-genetic component of variance is not the dominating term in the total genetic component occur rarely. This does, however, not imply that epistasis is irrelevant because functional epistasis typically generates additive effects, hence contributes to the additive variance.

4.1. The breeder's equation

With the help of the heritability, the response to selection in breeding experiments can be predicted. Let $\bar{P}$ and $\bar{P}_s$ denote the mean phenotype before and after selection. Because the environment contributes only white noise, we have $\bar{P} = \bar{G}$. The so-called *breeder's equation* states that the selection response across generations is

$$\Delta\bar{P} = h^2(\bar{P}_s - \bar{P})\,. \tag{4.4}$$

It can be derived without recourse to detailed genetic assumptions, simply by regressing offspring values on mid-parent values. This is based on the assumptions that there are no non-genetic causes for resemblance of relatives and that the regression is indeed linear (see Bulmer 1980, and Gimelfarb and Willis 1994 for discussion). Nevertheless, systematic departures from (4.4) apparently require quite extreme assumptions (Turelli and Barton 1994). The importance of the breeder's equation arises from the fact that it allows predictions of the selection response from readily measurable quantities.

4.2. The Secondary Theorem of Natural Selection

Assuming a linear offspring-parent regression, Robertson (1966, 1968) extended the breeder's equation to predict the correlated response caused by overall (artificial and natural) selection:

$$\Delta\bar{G} = \mathrm{Cov}_A(G, W)/\overline{W}\,. \tag{4.5}$$

Here, $W = W(G)$ denotes the fitness of individuals with genotypic value G, and $\mathrm{Cov}_A(G, W)$ is the additive genetic covariance of G and W (for precise definitions see Nagylaki 1993 or Bürger 2000, Chap. II.3). This is sometimes called the Secondary Theorem of Natural Selection and is closely related to the Li-Price equation (2.20).

Nagylaki (1993) extended this result and derived an asymptotic version from first principles and in great generality. He admitted arbitrary dominance and epistasis, both at the level of the trait and of fitness, but assumed that selection is weak relative to recombination ($s \ll c_{\min}$ in the notation of Section 3). He proved

$$\Delta\bar{G} = \mathrm{Cov}_A(G, W)/\overline{W} + O(s^2)\,, \quad t \geq t_2\,, \tag{4.6}$$

where t_2 is defined as in Theorem 3.3. If $G = W$, then (3.17) is obtained.

These are important results that provide deep insight into the way how quantitative traits respond to selection. However, they can not necessarily be used to predict evolutionary trajectories for several or many generations because $\mathrm{Cov}_A(G, W)$ and $\overline{W}$ may and will change under selection. Moreover, if there is epistasis and either selection is strong or linkage disequilibria are large, changes in the linkage disequilibria can induce large changes in $\bar{G}$ even if $\sigma_A^2 = 0$ (e.g., Gimelfarb 1989, Nagylaki 1993).

4.3. Lande's equation and multivariate evolution

In nature, and often also in breeding programs, selection acts on several or many traits. To study the evolution of multivariate phenotypes, Lande (1979) developed a theory for the evolutionary dynamics. The phenotype of an individual is characterized by a vector of measurements of K quantitative traits, $P = (P_1, \ldots, P_K)^T$. It is assumed to be determined by an additive genetic component G and an environmental component E such that $P = G + E$, where the mean of E vanishes. Hence, the mean vectors satisfy $\bar{P} = \bar{G}$. Lande's central, empirically testable, assumption is that the distributions of G (sometimes called the breeding values) and of E are both multivariate normal and independent. If the corresponding covariance matrices are denoted by $\mathbf{P}$, $\mathbf{G}$, and $\mathbf{E}$, then $\mathbf{P} = \mathbf{G} + \mathbf{E}$ holds. If the fitness of individuals with phenotype P is $W(P)$ and $f(P)$ denotes the (Gaussian) density of phenotypes, the mean fitness of the population is $\overline{W} = \int f(P)W(P)dP$, which is a function of $\bar{P}$ and $\mathbf{P}$.

Lande showed that the change of the mean phenotype between generations is

$$\Delta\bar{P} = \mathbf{G}\nabla \ln \overline{W} = \mathbf{G}\left(\frac{\partial \ln \overline{W}}{\partial \bar{P}_1}, \ldots \frac{\partial \ln \overline{W}}{\partial \bar{P}_K}\right)^T\,, \tag{4.7}$$

where $\nabla \ln \overline{W}$ is called the selection gradient. In the univariate case, this can be shown to be equivalent to Robertson's equation (4.5). Also the analogy to the Svirezhev-Shahshahani gradient (2.18) is notable. Moreover, it can be shown that (4.7) implies

$$\Delta \ln \overline{W} \geq 0\,, \tag{4.8}$$

and mean fitness is (strictly) increasing except at equilibria.

Lande's theory integrated quantitative-genetic models and methods into evolutionary genetics and had a huge impact on evolutionary biology. It has received innumerable applications and is of great heuristic and predictive value. Equation (4.7) also reveals that selection on ignored correlated traits may greatly obscure the selection response of the trait(s) under consideration (Lande and Arnold 1983).

Lande also established the powerful integrative concept of an adaptive landscape for phenotypic traits. (A related concept for genotypes had been introduced by Wright in 1931.) The adaptive landscape summarizes the selection pressures that act on a *population* and direct its evolution. Its height represents the mean fitness of the population as a function of the mean phenotype. Its slope and curvature determine the strength of directional and stabilizing selection, respectively. Equation (4.7) shows that the population mean evolves upwards on this surface, toward an adaptive peak. The precise direction is given by $\mathbf{G}$ (the so-called $\mathbf{G}$ matrix) and is usually not perpendicular to the level surfaces. Ecological change can be captured by models of peak movement (for a review, see Arnold et al. 2008).

The strength and attractiveness of Lande's theory arises from the simple and intuitive nature of his equation and from the fact that no detailed genetic information is necessary (though measuring W and $\mathbf{G}$ in natural populations is usually cumbersome and laborious). The derivation of Lande's equation does not specify the mechanisms that maintain variation and, in order to predict the evolutionary response for more than one generation, a constant $\mathbf{G}$-matrix has to be assumed. In particular, this assumption of constancy has been criticized severely because, in general, $\mathbf{G}$ evolves and predicting its evolution is difficult (e.g., Turelli 1988).

In the meantime, the stability properties of the $\mathbf{G}$-matrix have been investigated using individual-based simulations of explicit multilocus models that include recurrent pleiotropic mutation. For a constant and for a moving peak, conditions have been identified when a bivariate $\mathbf{G}$-matrix (or some if its characteristics such as its total size, or shape, or orientation) remains approximately stable despite random genetic drift (e.g., Jones et al. 2003, 2004; see Arnold et al. 2008 for a comprehensive review). Also substantial effort has been devoted to derive the evolution of the whole distribution of genotypic values under general selection scenarios. Due to the inherent complexity, these approaches were mainly restricted to univariate traits and we discuss them below.

4.4. The evolutionary dynamics derived from genetic principles

The derivation of the evolutionary dynamics of a quantitative trait from genetic principles is a complex enterprise that faces severe difficulties. The focus has been on equations for the mean, the variance, and the higher moments under the assumption that the trait is determined additively by finitely many loci (Barton and Turelli 1987, 1991; Turelli and Barton 1990; Bürger 1991). A comprehensive account of the theory is given in Chap. V of Bürger (2000).

Kirkpatrick et al. (2002) developed further generalizations and implemented a computer algebra package to handle the recursions.

Here, we present only two results that complement the above theory and can be formulated easily. We represent the fitness function acting on the genotypic values G as a Taylor series,

$$W(G) = \sum_{j=0}^{\infty} s_j G^j \,. \tag{4.9}$$

(Since E has a normal distribution, the coefficients of $W(G)$ are straightforwardly calculated from the series expansion of $W(P)$.) No assumptions about the distribution of allele frequencies, of genotype frequencies, or of breeding values are made.

The distribution of G evolves as a result of the interaction of selection, mutation, recombination, and random mating. For simplicity, we assume that the distribution of mutational effects is symmetric with respect to the mean. Let us denote by M_j^0 the jth moment around zero of the distribution of G and by C_j its jth cumulant; thus, $C_1 = \bar{G}$ and $C_2 = \sigma_A^2$. Because of their additivity property, cumulants are particularly useful to describe the effects of selection on an additive trait (Bürger 1991).

Then the response of the mean phenotype can be written in each of the following ways:

$$\Delta\bar{G} = \frac{1}{\overline{W}} \operatorname{Cov}_A(G, W) \tag{4.10a}$$

$$= \frac{1}{\overline{W}} \sum_j s_j M_{j+1}^0 - \bar{G} \tag{4.10b}$$

$$= s_1\sigma_A^2 + s_2(C_3 + 2\bar{G}\sigma_A^2) + s_3(C_4 + 3\bar{G}C_3 + 3\sigma_A^4 + 3\bar{G}^2\sigma_A^2) + \ldots \tag{4.10c}$$

$$= \sigma_A^2 \frac{\partial \ln \overline{W}}{\partial \bar{G}} + C_3 \frac{\partial \ln \overline{W}}{\partial \sigma_A^2} + C_4 \frac{\partial \ln \overline{W}}{\partial C_3} + \ldots \,. \tag{4.10d}$$

Explicit formulas instead of the dots can be given. Obviously, the first equation is Robertson's (4.5). If the distribution of G is Gaussian, the last equation yields the univariate version of Lande's (4.7) because then all cumulants of order three and higher vanish. The terms $\partial \ln \overline{W}/\partial C_k$ are called (higher-order) selection gradients.

Equations (4.10) show that, in general, the evolutionary dynamics depends not only on the variance, but also on the higher moments or cumulants of the distribution of breeding values. Importantly, however, the response of the mean does not depend on genetic details, such as number of loci, the distribution of allelic effects at particular loci, or the linkage map.

This changes dramatically when the dynamics of the higher moments is studied. We confine our attention to the additive genetic variance. Its change depends not only on all pairwise recombination rates and the mutation distribution at individual loci, but also on all pairwise linkage disequilibria

and even on the pairwise associations between loci at homologous gametes within an individual that are generated by selection (see p. 194 in Bürger 2000). Under the assumption of quasi-linkage equilibrium, which is fulfilled if selection is weak relative to recombination and $t \geq t_2$ (Result 3.3), the change of σ_A^2 across generations is given by

$$\Delta\sigma_A^2 = s_1 C_3 + s_2 \left(C_4 + 2\bar{G} C_3 + 4 \sum_{n=1}^{L} \kappa_{nn} \right) + \ldots + 2 \sum_n \mu_n \gamma_n^2 + O(s^2) \,. \tag{4.11}$$

Here, κ_{nn} designates the second cumulant (= variance) of the distribution of allelic effects at locus n, μ_n is the haploid mutation rate of locus n, γ_n^2 is the variance of mutational effects at locus n, and s may be defined as $s = \sum_j |s_j|$.

Equation (4.11) shows that, unless selection is linear ($s_j = 0$ if $j \geq 2$), the response of the variance depends on higher cumulants and on genetic details. Even for equivalent loci, when $\sum_{n=1}^{L} \kappa_{nn} = \frac{1}{L}\sigma_A^4$, the number L of loci needs to be known to predict the variance. (The total input of mutational variance per generation, $2\sum_n \mu_n \gamma_n^2$, is relatively easy to estimate from mutation-accumulation experiments.) These complications underly and explain the skepticism that has been articulated, especially by Turelli, against the use of Lande's (or any other existing) theory for inferences about long-term evolution. Nevertheless, some positive results have been obtained (e.g., Turelli and Barton 1994; Bürger and Lande 1994; Bürger 2000, Chap. VII; Reeve 2000; Jones et al. 2003, 2004).

The above results are based on the assumption that allelic effects contribute additively, i.e., without dominance and epistasis, to the trait. However, because the fitness function may and usually will be nonlinear, dominance and epistasis in fitness is included and not necessarily weak.

Little is known about the genotype-phenotype map, except that it is exceedingly complex. The quantitative genetics approach to treat epistasis as a statistical deviance from additivity has been highly successful, but makes epistasis more a population property than a property of the functional interaction among genes. A systematic approach to develop a population-genetic framework for studying the role of functional epistasis has been pioneered by Hansen and Wagner (2001); see Zhivotovsky and Gavrilets (1992) for a progenitor. Based on this and a very similar model, interesting consequences for the evolution of quantitative traits were derived by Hermisson et al. (2003) and by Barton and Turelli (2004).

4.5. Maintenance of genetic variation

So far, we have not said anything about how genetic variation is maintained. As outlined in Ewens' chapter, this problem already plagued Darwin. Although Mendelian inheritance solves part of the problem, a satisfactory quantitative resolution has not yet been achieved. Many facts and open questions contribute to this failure. First, there is plenty of genetic variation in quantitative traits. For instance, heritabilities are typically in the range of 20% - 50%, and short-term and long-term selection responses can be enormous.

Second, many forms of selection, especially the commonly observed stabilizing selection and most forms of directional selection, tend to deplete genetic variation. Third, mutation is the ultimate source of genetic variability, and recombination disperses variability greatly, but models of mutation-selection balance can, in general, account only for a fraction of the empirically observed heritabilities. However, a final answer will not be possible before we understand the nature of quantitative genetic variation, especially the roles of regulatory versus structural genes much better (see Bürger 2000 for a comprehensive treatment of this topic, and Barton and Keightley 2002 for a more recent review).

High levels of genetic variation can be maintained under various forms of balancing selection, which may be caused by migration-selection balance, genotype-environment interaction, frequency-dependent selection, or pleiotropy (e.g., Turelli and Barton 2004; Zhang et al. 2004; Bürger 2005; Schneider 2006, 2010; Nagylaki and Lou 2007; Nagylaki 2009; Bürger 2009b, 2010). However, none of these explanations is universally applicable, and quantitative predictions require not only information about the genetic basis of the trait(s), but also detailed ecological knowledge about the population.

5. Fundamental topics omitted

There are a number of fundamental topics in evolutionary genetics that have not even been mentioned above. These include speciation (see Gavrilets 2004 for a fairly recent account focusing on theory), the evolution of sex and recombination (for a brief and recent review, see Otto 2009), and molecular evolution.

As mentioned in the Introduction, stochastic models have been of paramount importance since the early work of Fisher and Wright. Essential further developments are due to Malécot and Kimura, who established the method of diffusion approximation as a powerful tool for the study of the evolutionary dynamics under the influence of random genetic drift. Kimura (1983) also advocated the neutral theory of evolution which, upon modification and extension, has become one of the corner stones of evolutionary and population genetics. This, and much more, work is comprehensively covered by Ewens (2004).

More recently, the focus in population genetics has changed to study evolution backward in time. This line of work was motivated by the desire to infer the evolutionary history of species from molecular data of extant populations. It has been fueled by the increasing availability of dense maps of genetic markers and sequence data which, under certain conditions, allow the reconstruction of ancestral relationship and past evolutionary events. Its mathematical ancestor is Kingman's coalescent process. For a beautiful treatment consult Wakeley (2008).

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