

Article

Dynamics of Polygenic Adaptation

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Abstract

Polygenic adaptation in response to natural selection on a quantitative trait has become an important topic in population genetics and evolution. We modeled a scenario in which a population was assumed to be in equilibrium between mutation, selection and genetic drift, when a sudden shift in the fitness optimum occurred. It is well known that after an environmental shift the trait mean may approach the new optimum very quickly at a rate proportional to the equilibrium genetic variance. Here, we analyze the dynamics of the allele frequencies at individual loci, using diffusion theory. We show that genetic drift slows down the speed of polygenic adaptation. We also found that, while the frequencies of rare and very common alleles decrease during the adaptive phase, alleles starting at intermediate equilibrium frequencies at the time of the optimum shift change most quickly and thus may substantially modify the shape of the allele frequency distribution. Finally, we explain how these properties of the allele frequency spectrum may be utilized in statistical tests of polygenic selection.

Keywords: polygenic selection; rapid adaptation; quantitative trait; allele frequency spectrum

MSC: 60J60

1. Introduction

Evolutionary adaptation is the process that natural populations experience to become suited to their environment. Adaptation is driven by natural selection. For more than a century population geneticists have developed mathematical models to describe this process [1]. In most cases selection is assumed to act at single loci (genes). However, extensions of single-locus models to multi-locus models were also considered. In recent years, due to the advance of genome-wide association studies (GWASs), polygenic selection was studied using models from quantitative genetics that are formulated in terms of allele frequency changes. In contrast to the single- and multi-locus cases, in polygenic models selection acts on a phenotypic trait, and a genotype–phenotype map is assumed to bridge the gap to population genetics. Polygenic models usually include a very large number of selected loci that control a phenotype [2].

Polygenic adaptation driven by a large number of weakly selected loci is not nearly as well studied as the case of strong positive selection leading to selective sweeps [3]. However, reviews by Pritchard et al. [4] and Pritchard and Di Rienzo [5] drew the attention of population geneticists to this type of selection. De Vladar and Barton [6] and Jain

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and Stephan [7] used a deterministic model to analyze the dynamics of adaptation after a sudden environmental shift in the fitness optimum of a phenotypic trait in the absence of genetic drift. According to Jain and Stephan [8,9], this model predicts that rapid adaptation may occur either through strong directional selection at a few loci (when the effect sizes of the alleles at these loci are large, relative to a scaled mutation rate), through weak selection at many loci with small effect sizes or through a combination of these two processes. In the case of many loci with small effects subtle allele frequency shifts are typical. However, all these studies assumed infinitely large population sizes. This led to problems in defining the values of the allele frequencies at the time of the environmental change, as the equilibrium allele frequencies of the deterministic model do not agree with the frequencies typically observed in GWAS. Recognizing this problem, the studies published in the past few years [10–14] include genetic drift (due to finite population size) into their polygenic models.

Simons et al. [12] proposed a model of selection that simultaneously acts on multiple traits (pleiotropy). Stetter et al. [13] and Thornton [14] analyzed a model that also includes neutral loci linked to selected ones. Stetter et al. also investigated the effect of different demographies and genetic architectures of the trait. In the model of Höllinger et al. [10] the loci controlling a trait are not explicitly given, but instead a genome-wide mutation rate is used as a proxy. Their main conclusions on the modes of rapid adaptation, however, are very similar to the predictions of Jain and Stephan [8] mentioned above.

The goal of this paper is to continue the theoretical work started by John and Stephan [11] on polygenic adaptation. In the latter study we analyzed the case of a natural population before the environment changes and the fitness optimum of a trait shifts to a new value. We assumed that up to this timepoint the population was in equilibrium between mutation, selection and genetic drift. Now, we would like to understand how the population responds to the change in the fitness optimum, based on an analytical treatment of the original model of de Vladar and Barton [6] and genetic drift. We follow the dynamics of the trajectories of the allele frequencies in the early phase of polygenic adaptation starting at the timepoint when the fitness optimum of the population has suddenly shifted to a new value. This early time window does not encompass the entire adaptive phase (until the population has adapted to the new fitness optimum), yet it is important, as it provides insights into recent observations of biologists that are usually concerned with rapid adaptation shortly after an environmental shift (i.e., between about tens to a hundred generations). We specifically analyze the simulation data published by Stephan and John [15] using diffusion theory. To accomplish this, we needed to solve a system of ordinary differential equations for the lowest-order moments of allele frequencies.

Examples of rapid adaptation in response to changes that are natural or due to human activity include color variation in guppies [16], field mice [17] and peppered moth [18], as well as insecticide resistance in *Drosophila* [19]; beak size changes in Darwin's finches [20], and limb development in *Anolis* lizards [21]. Clearly, not all these examples of fast adaptation are polygenic. Color variation in peppered moths appears to be due to one or a few major genes [22] and insecticide resistance studied by Ffrench-Constant et al. [19] as well. However, others are highly polygenic, such as human height [23]. It was suggested that human height is controlled by more than 500 genes, although recent estimates have shown that this number is probably too high since population structure has not been adequately considered in data analysis [24,25]. Here, we use parameter estimates inferred from the human height study by Turchin et al. [23] for our numerical examples, assuming that about 200 genes are involved in the evolution of this trait.

2. Model

We consider a perfectly heritable trait that is controlled additively (no dominance or epistasis) by n unlinked, diallelic loci in a very large population of diploids. If the phenotypic effect of the trait-increasing allele, also called + allele, at locus i is $\frac{\gamma_i}{2}$ and that of the − allele is $-\frac{\gamma_i}{2}$, the mean phenotype c_1 , the genetic variance c_2 and the skewness c_3 are given by [8]

$$c_1 = \sum_{i=1}^n \gamma_i (p_i - q_i) = \sum_{i=1}^n \gamma_i (2p_i - 1), \quad (1)$$

$$c_2 = 2 \sum_{i=1}^n \gamma_i^2 p_i q_i, \text{ and} \quad (2)$$

$$c_3 = 2 \sum_{i=1}^n \gamma_i^3 p_i q_i (q_i - p_i), \quad (3)$$

where p_i is the frequency of the + allele at locus i and $q_i = 1 - p_i$ is that of the − allele. We assume that the effect sizes are exponentially distributed with mean $\bar{\gamma}$. Furthermore, the fitness of an individual with trait value z has a Gaussian shape centered about the fitness optimum, which in equilibrium is denoted by z_0 . Thus,

$$w(z) = e^{-\frac{s}{2}(z-z_0)^2}, \quad (4)$$

where s measures the strength of selection on the trait and $1/s$ is assumed to be much larger than the phenotypic variance [12]. We also assume $0 < z_0$, and require that $z_0 < n\bar{\gamma}$. The latter condition ensures that—after perturbation—the population mean converges to a stationary state close to the optimum [7]. In a randomly mating population, the change in allele frequency at the i th locus due to selection and mutation is then given by

$$\frac{dp_i}{dt} = -s\gamma_i p_i q_i \Delta c_1 - \frac{s\gamma_i^2}{2} p_i q_i (q_i - p_i) - \mu(p_i - q_i), \quad i = 1, \dots, n, \quad (5)$$

where $\Delta c_1 = c_1 - z_0$ is the deviation of the mean phenotype from the fitness optimum. The first term on the right-hand side of Equation (5) describes directional selection toward the phenotypic optimum, the second term accounts for stabilizing selection in the neighborhood of the optimum [26], and the last term for symmetric mutation between the + and − alleles [27], where μ is the mutation rate.

De Vladar and Barton [6] presented an analytical treatment of the equilibrium properties of the above model. They found that the alleles may be classified into those with effects smaller than a threshold value $\hat{\gamma} = 2\sqrt{\frac{2\mu}{s}}$ (minor alleles) and those with larger sizes (major alleles). Since we model polygenic adaptation, we assume in this paper that effect sizes are smaller than the threshold value $\hat{\gamma}$.

This model is different from the so-called infinitesimal model, which is also widely used (e.g., [28,29]). In the latter model a large number of loci with very small effects control a quantitative trait such that the equilibrium genetic variance is independent of the number of loci. In contrast, in our model we assume that the effect sizes do not change with the number of loci, but the variance may change substantially. On the other hand, the pleiotropic model of Simons et al. [12] mentioned in Introduction is identical to ours, if only a single trait is considered.

2.1. Stochastic Equilibrium Between Genetic Drift, Mutation and Selection

In this section we consider biologically more realistic conditions for adaptation than above by integrating genetic drift into our deterministic model. We assume that the (diploid) population size is N , which is constant. In John and Stephan [11] we have shown that in the stochastic equilibrium between genetic drift, mutation and selection, the population mean is fluctuating around a state close to the fitness optimum z_0 (but not identical to z_0).

Since in the deterministic case the trait mean may change much faster after a perturbation than the allele frequencies [7], we expressed Equation (5) as follows to analyze the equilibrium fluctuations:

$$\frac{d\Delta c_1}{dt} = -\frac{s}{2}c_3 - sc_2\Delta c_1 - 2\mu c_1 \quad (6)$$

and

$$\frac{dp_i}{dt} = -s\gamma_i p_i q_i \Delta c_1 - \frac{s\gamma_i^2}{2} p_i q_i (q_i - p_i) + \mu(q_i - p_i). \quad (7)$$

Equation (6) was derived by summing over Equation (5) and using the definitions of the cumulants (Equations (1)–(3)). Since in the case of rapid evolution Δc_1 is a fast variable on the time scale of the allele frequencies p_i , we obtained $\Delta \tilde{c}_1$ by putting the left-hand side of Equation (6) to zero ([30], Chapter 6.4). Then, in quasi-equilibrium the deviation of the population mean from z_0 is approximately

$$\Delta \tilde{c}_1 \approx -\frac{\frac{s}{2}c_3 + 2\mu z_0}{s\tilde{c}_2 + 2\mu}, \quad (8)$$

where tilde indicates the quasi-equilibria of the cumulants involved. The variance is relatively constant [7]. The skewness term varies with time but may be very small if we assume that the effect sizes are small (Equation (3)). Equation (8) predicts that in equilibrium the trait mean is not identical to but is very close to the fitness optimum, because in this model the allele frequencies of Equation (5) approach stable equilibrium states that are incompatible with the fitness optimum ([6], Figure 2A and Appendix B).

Using Equation (8), the expected change in the allele frequency p_i may be approximated as

$$E\{\Delta p_i\} \approx -s\gamma_i p_i q_i \Delta \tilde{c}_1 - \frac{s\gamma_i^2}{2} p_i q_i (q_i - p_i) + \mu(q_i - p_i), \quad (9)$$

where $\Delta \tilde{c}_1$ is assumed to be constant. Furthermore, the variance of the change in p_i accounting for the effect of genetic drift is

$$\text{Var}\{\Delta p_i\} \approx \frac{p_i q_i}{2N}. \quad (10)$$

Using diffusion theory ([31], Chapter 4.5), this leads to the equilibrium frequency distribution of the trait-increasing allele p_i at locus i :

$$f(p_i) \approx C_i p_i^{2\beta-1} q_i^{2\beta-1} \exp(-2\alpha\gamma_i \Delta \tilde{c}_1 p_i - \alpha\gamma_i^2 p_i q_i), \quad (11)$$

where C_i is the normalization constant, $\alpha = 2Ns$, and $\beta = 2N\mu$ is the scaled mutation rate.

We compared the theoretical results with simulations using the following set of parameter values: $s = 0.1$, $N = 2 \times 10^4$, $n = 200$, $\mu = 10^{-5}$, and $\bar{\gamma} = 0.01$. These values were taken from the literature on polygenic adaptation in humans in particular human height [12,23]; the value for the optimum z_0 was chosen such that $z_0 = 0.2 < n\bar{\gamma}$. We found an excellent agreement of theoretical predictions with the simulation results [32]. Here, we

use these parameter values for comparing our analytical approximations with published simulation results (see next section).

An important difference to the deterministic model is that in our stochastic analysis the equilibrium is given as a probability distribution of allele frequencies (Equation (11)), not as a single value (as in the deterministic model). For very large populations this distribution is bell-shaped if $\beta > 0.5$ ([31], Chapter 5.6). However, for our set of biologically realistic parameter values we obtained a U-shaped distribution (Figure 1, [32]). The reason is that in equilibrium the genetic variance for exponentially distributed effect sizes with mean $\bar{\gamma}$ is approximately

$$\tilde{c}_2 \approx \frac{4\beta}{4\beta+1} n\bar{\gamma}^2 \quad (12)$$

rather than $n\bar{\gamma}^2$ as for the deterministic case [17].

2.2. Adaptive Phase

To model adaptation to the new fitness optimum, we assume that a population is in equilibrium when the fitness optimum z_0 is suddenly shifted to a new value $z_f > z_0$, where $z_f < n\bar{\gamma}$. As explained in the previous section, since the trait mean responds rapidly to the shift in the fitness optimum, it may be approximated by an exponential process whose rate is proportional to the equilibrium genetic variance at the time of the environmental shift in the optimum [29]:

$$\Delta c_1(t) \approx \Delta c_1(0) \exp(-sc_2(0)t), \quad (13)$$

where $\Delta c_1(0) = z_0 - z_f$. The variable t measures time in generations such that $t = 0$ is the timepoint when the fitness optimum shifts to its new value.

Equation (13) characterizes the short-term phase of polygenic adaptation [8]. The short-term phase is the time until the phenotypic mean reaches a value close to the new fitness optimum. It lasts about $1/(sc_2(0))$ generations. Thus, it may be very short when the variance at the shift in the fitness optimum is large. As suggested by Equation (12), this is the case when the number of loci controlling the trait is large and/or the scaled mutation rate β is not too small.

Next, we investigate the effect of drift on the dynamics of allele frequencies in the adaptive phase. In the short-term phase, i.e., the time until the phenotypic mean reaches a value close to the new optimum, ODE (5) can be approximated by [7,8]

$$\frac{d}{dt} p_i = -s\gamma_i \Delta c_1(t) p_i q_i, \quad (14)$$

where $\Delta c_1 = c_1 - z_f$, i.e., in the rapid initial phase when the population is far from the new fitness optimum stabilizing selection and mutations are much less important than directional selection.

To describe the changes in the frequencies of the trait-increasing alleles p_i stochastically, we use a diffusion approximation (similar to the approach in [33]). The differential operator $\mathcal{L}_i$ of the Kolmogorov backward equation is

$$\mathcal{L}_i = \left(-s\gamma_i p_i (1 - p_i) \Delta c_1(t) \right) \frac{\partial}{\partial p_i} + \frac{p_i(1-p_i)}{4N} \frac{\partial^2}{\partial p_i^2}. \quad (15)$$

As in Equation (14), the first term of this operator includes only the effect of directional selection. Using Equation (15), we obtain ODEs for the two lowest-order moments of the allele frequencies as

$$\frac{d}{dt} E\{p_i\} = -s\gamma_i E\{p_i(1 - p_i)\} \Delta c_1(t) \quad \text{and} \quad (16)$$

$$\frac{d}{dt}E\{p_i^2\} = -2s\gamma_i E\{p_i^2(1-p_i)\}\Delta c_1(t) + \frac{1}{2N}E\{p_i(1-p_i)\}. \quad (17)$$

Combining these two ODEs yields

$$\frac{d}{dt}E\{p_i(1-p_i)\} = -s\gamma_i E\{p_i(1-p_i)\}\Delta c_1(t) + 2s\gamma_i E\{p_i^2(1-p_i)\}\Delta c_1(t) - \frac{1}{2N}E\{p_i(1-p_i)\}. \quad (18)$$

Before solving this system of ODEs it is helpful to consider the deterministic case based on Equation (14). The solution of Equation (14) is approximately [7]

$$p(t) \approx \frac{p(0)}{p(0)+q(0)\exp\left[\frac{\gamma\Delta c_1(0)}{c_2(0)}(1-e^{-sc_2(0)t})\right]}. \quad (19)$$

Here, and in the following, index i is omitted. For short times (i.e., $sc_2(0)t \ll 1$ and $s\gamma\Delta c_1(0)t \ll 1$), this formula can be written as

$$p(t) \approx p - s\gamma p q \Delta c_1(0)t, \quad (20)$$

where p and $q = 1 - p$ denote the initial conditions $p(0)$ and $q(0)$, respectively, at the time of an environment change. This approximation does not encompass the entire adaptive phase as defined above. However, the initial linear part of it is included, which is important as most studies on rapid adaptation (in the field or laboratory) are only concerned with short time intervals (see Introduction).

Next, we derive a formula for $E\{p(t)\}$ using our stochastic approach (Equations (15)–(18)). We begin solving ODE (18). The system of ODEs (16) and (18), however, cannot be solved in a closed form as the moment expansion does not break up. Therefore, we suggest writing for short times (i.e., $sc_2(0)t \ll 1$ and $s\gamma\Delta c_1(0)t \ll 1$)

$$E\{p^2(t)(1-p(t))\} \approx E\{p(0)p(t)(1-p(t))\} = pE\{p(t)(1-p(t))\}, \quad (21)$$

since for short times $p(t) \approx p(0) = p$. This leads to

$$E\{p(t)q(t)\} \approx pq \exp\left[-s\gamma\Delta c_1(0)(1-2p)t - \frac{t}{2N}\right]. \quad (22)$$

Inserting (22) into ODE (15) and using Formula (13) for $\Delta c_1(t)$, we obtain for small t values

$$E\{p(t)\} \approx p - s\gamma p q \Delta c_1(0)t. \quad (23)$$

Thus, for short times our deterministic and stochastic treatments lead to identical results.

To calculate the average trajectory $\bar{p}(t)$ of + alleles for short times after an environmental change we combine Equation (23) with the equilibrium distribution (11). Since the exponential function in (11) can be linearized for the parameter values $N = 2 \times 10^4, 10^4, 5 \times 10^3, s = 0.1, \gamma = 0.01, n = 200, \mu = 10^{-5}, z_0 = 0.2, z_f = 0.5$ used in this study, we obtain from Equation (A2) in Appendix A

$$\bar{p}(t) = \int_0^1 E\{p(t)\}f(p) dp \approx a - b \cdot s\gamma\Delta c_1(0)t, \quad (24)$$

where

$$a = C^{-1}[B(2\beta + 1, 2\beta) - 2\alpha\gamma\Delta\tilde{c}_1 B(2\beta + 2, 2\beta) - \alpha\gamma^2 B(2\beta + 2, 2\beta + 1)], \quad (25)$$

$$b = C^{-1}[B(2\beta + 1, 2\beta + 1) - 2\alpha\gamma\Delta\tilde{c}_1 B(2\beta + 2, 2\beta + 1) - \alpha\gamma^2 B(2\beta + 2, 2\beta + 2)] \quad (26)$$

and C^{-1} is given by Equation (A3) of Appendix A.

Table 1 contains numerical values for a and b calculated from Formulas (24)–(26):

Table 1. Numerical values of a and b for various population sizes.

N	$\Delta\tilde{c}_1$	a	b
2×10^4	−0.0022	0.516	0.151
10^4	−0.0030	0.516	0.110
5×10^3	−0.0046	0.516	0.071

For $N = 2 \times 10^4$ we used $\Delta\tilde{c}_1 = -0.0022$, which was obtained by simulation [11]. The $\Delta\tilde{c}_1$ values for the smaller population sizes $N = 10^4$ and 5×10^3 were calculated from Equation (8), in which $\frac{s}{2}\tilde{c}_3$ is neglected, as effect sizes are small. Furthermore, Equation (12) was used.

The increase in b with population size N suggests that genetic drift slows down polygenic adaptation. To understand the effect of drift in more detail, we will compare these results with our simulation data for $\bar{p}(t)$ shown in Figure 2 of Stephan and John [15]. In the simulations we used the same parameter values as in the theoretical calculations. Table 2 shows that the agreement of simulations and theory is quite good for small times (up to 500 generations) when population sizes are relatively small (up to 10^4 individuals). However, discrepancies between theory and simulations are observed for $N = 2 \times 10^4$, such that the simulation results exceed the theoretical predictions (Table 2).

Table 2. Simulation data of Stephan and John [15] and comparison with theory.

t	$N = 2 \times 10^4$		$N = 10^4$		$N = 5 \times 10^3$	
	$-\tilde{b}t$	$\bar{p}(t) - \bar{p}(0)$	$-\tilde{b}t$	$\bar{p}(t) - \bar{p}(0)$	$-\tilde{b}t$	$\bar{p}(t) - \bar{p}(0)$
100	0.0045	0.0067	0.0033	0.0056	0.0021	0.0015
200	0.0091	0.0137	0.0066	0.0068	0.0043	0.0055
300	0.0136	0.0213	0.0099	0.0110	0.0064	0.0080
400	0.0181	0.0242	0.0132	0.0133	0.0085	0.0086
500	0.0227	0.0279	0.0165	0.0161	0.0107	0.0100

The first column denotes the time t (in generations) since the fitness optimum changed. In the second, fourth and sixth columns the theoretical values (Equation (24)) are shown with $\tilde{b} = bs\gamma\Delta c_1(0)$. The third, fifth and seventh columns denote the simulation data as $\bar{p}(t) - \bar{p}(0)$ for populations of size $N = 2 \times 10^4$, 10^4 and 5×10^3 , respectively. The other parameter values used in the simulations are: $s = 0.1$, $\gamma = 0.01$, $n = 200$, $\mu = 10^{-5}$, $z_0 = 0.2$, $z_f = 0.5$. The simulations were run for $2N$ generations until from $t = 0$ on data were recorded [15].

We first note that the mean allele frequencies at $t = 0$ are (nearly) identical and thus independent of population size (Table 1). Furthermore, they are slightly larger than 0.5, which is the value expected under neutrality ([31], Chapter 5.6). This difference reflects the slight bias of the equilibrium distribution toward larger allele frequencies due to positive selection (Equation (11)). Second, the linear increase of $\bar{p}(t)$ for small t values, however, depends strongly on population size, such that larger populations show a steeper slope. The reason is that for the smaller populations the equilibrium allele frequency distribution is sharply U-shaped, whereas for larger populations the distribution is more centered in the intermediate-allele frequency range. Alleles starting at $t = 0$ in this middle range are less subjected to drift and thus contribute more to polygenic adaptation, which is reflected by a steeper increase in the adaptive trajectories for small t values (Table 1). This was already observed in the simulations of John and Stephan [17]. Finally, to understand the discrepancy between theoretical and simulation results that is particularly apparent for the larger population size $N = 2 \times 10^4$, we may compare Figure 3 in John and Stephan [11] with Figure 1 in Stephan [32]. In the older figure in [11], the allele frequency distribution is recorded after $2N$ generations, which corresponds to

timepoint $t = 0$ of Figure 2 in Stephan and John [15]. Comparing Figure 3 in John and Stephan [11] with Figure 1 in Stephan [32], for which the simulation data were recorded after $3N$ generations, clearly suggests that after $2N$ generations equilibrium was not reached in the simulations, such that an excess of counts is observed for intermediate frequencies. As a consequence, the simulated $\bar{p}(t)$ values are expected to exceed the theoretical predictions. For the two smaller populations discrepancies between theory and simulations can only be seen for t values ≤ 300 generations (Table 2), i.e., at timepoints closer to $t = 0$, not for $t = 400$ or 500 . This may therefore also be because equilibria have not yet been reached. This hypothesis is supported by the observation that for all three population sizes $\bar{p}(0)$ is smaller than the theoretically predicted value $a = 0.516$ (Table 1).

The effect of genetic drift on the dynamics of allele frequencies in the adaptive phase can be even more clearly demonstrated by comparing $\bar{p}(t)$ averaged over all trajectories (as above) with those trajectories that originate in the corners of the frequency distribution of Equation (11). We focus here on very low allele frequencies $\leq p_0$ and denote the trajectories averaged over the interval $[0, p_0]$ as $\hat{p}(t)$. Using Equation (A4), $p_0 = 0.1$, and the parameter values $N = 2 \times 10^4$, $s = 0.1$, $\gamma = 0.01$, $n = 200$, $\mu = 10^{-5}$, $z_0 = 0.2$, $z_f = 0.5$, and $\Delta\tilde{c}_1 = -0.0022$, we find for the linear term

$$\hat{p}(t) - \hat{p}(0) \approx -0.044sy\Delta c_1(0)t, \quad (27)$$

which increases much more slowly than $\bar{p}(t) - \bar{p}(0)$: according to Table 1, $b = 0.151$ is almost four times as large as 0.044 . This suggests that many trajectories starting at very low frequencies ≤ 0.1 , where $p_0 = 0.1$ is an arbitrary cutoff for low-frequency alleles, are lost early in the adaptive phase due to genetic drift. Thus, summarizing this section, we found that trait-increasing alleles starting at the time of the shift in the fitness optimum from intermediate frequencies contribute most to changes in the trait mean, while many alleles starting at very low or very high frequencies get lost or fixed. This leads to a change in the allele frequency distribution relative to its shape at the time of the environment shift.

3. Discussion

In a previous paper we have presented analytical results on the equilibrium properties of a model of polygenic adaptation [11]. We modeled a scenario in which a population was assumed to be in equilibrium between mutation, selection and genetic drift, when a sudden shift in the fitness optimum occurred. Using these results, we present here a theoretical analysis of the adaptive phase, in which a quantitative trait responds to the shift in the fitness optimum, and discuss its evolutionary implications.

Based on Lande's [29] work it is well known that after an environmental shift the trait mean may approach the new optimum quickly at a rate proportional to the equilibrium genetic variance. However, little is known about the dynamics of allele frequencies at individual loci. Using diffusion theory, we show here that the trajectories of the allele frequencies in the adaptive phase depend strongly on their equilibrium distribution as well. We obtained explicit analytical results for the initial period of the adaptive phase in which exponential functions describing the allele trajectories can be linearized, and we compared these formulas with previously published simulation data. Since explicit results could only be derived by combining moments of the allele frequencies with the initial conditions predetermined by their equilibrium distribution, we could not obtain results for the entire adaptive phase, but only for the initial linear period of the trajectories. Nonetheless, it became very clear that genetic drift constrains polygenic adaptation mainly due to its effects in the equilibrium phase before the environmental shift in the fitness optimum occurs. We found that alleles with intermediate equilibrium frequencies

contribute most to changes in the trait mean (i.e., are aligned with the optimum shift). Also, in contrast, alleles with very low or high frequencies (at the time of the environment change) are subject strongly to genetic drift and thus may get lost or fixed as the trait mean approaches the new fitness optimum. Thus, we gained important insights into polygenic adaptation by analyzing a mathematical model. Clearly, this model has limitations, but—in the future—it could be extended to include assumptions on non-Gaussian selection, dominance, and linkage between loci.

Our findings will have some important implications for the detection of positive selection associated with polygenic adaptation. While in the polygenic case the effect of selection on individual loci is generally very weak and cannot be reliably detected, the collective impact across many loci can be estimated when their allele frequencies shift in the same direction after an environmental change [9]. Such a coordinated shift is predicted by the deterministic model [11]. However, in a finite population experiencing drift we found a more complex picture, namely that only for sufficiently large values of the parameter $p_i(0)q_i(0)$ the frequency shift in the trait-increasing allele at a locus i tends to occur in the same direction as the shift in the fitness optimum [11].

According to the results in this paper, the spectrum of allele frequencies may change in the adaptive phase. Statistical tests of selection for polygenic adaptation utilize this change in the shape of the allele spectrum during the adaptive phase. They are usually designed to detect signatures of such frequency changes either by comparisons across populations or across time within a population (species). The first study of polygenic selection was reported by Turchin et al. [23]. They analyzed GWAS data on human height between northern and southern Europeans. These populations have been separated from each other in the last ca. 100 generations. The authors show that trait-increasing alleles (+alleles) are significantly more frequent in northern populations (Sweden and UK) than in southern ones (Italy, Spain and Portugal). They conclude based on likelihood ratio tests that the observed frequency differences are better explained by a model that comprises both drift and positive directional selection rather than drift alone. A subsequent more formal analysis was presented by Berg and Coop [34]. They established a null model for how genetic scores should vary among populations under neutrality. More detailed null models have been constructed in further studies by incorporating information about historical population structure [35]. This allowed the authors to identify which branches in the coalescent experienced polygenic selection. A method to detect signatures of polygenic adaptation within a population across time was proposed by Field et al. [36]. It is based on the idea that a terminal branch of a coalescent is shorter for a beneficial allele than for a detrimental one. They applied their method to a population from Britain and found that the frequencies of height-increasing alleles from contemporary sequences increased significantly in the past 80 generations (ca. 2000 years) relative to those in the ancestors of modern Britons.

Interestingly, however, none of these methods—and to my knowledge also other more recent approaches for detecting polygenic selection—specifically take into account that intermediate-frequency alleles increase in frequency, while the frequencies of rare and very common alleles decrease during the adaptive phase. Such changes across all loci controlling a quantitative trait should be detectable using standard tests on the frequency spectrum such as Tajima's [37] D statistic and applying them across time or between populations.

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Appendix A

Appendix A.1. Derivation of an Equation for $\bar{p}(t)$

Using Equations (11) and (23), we write

$$\bar{p}(t) = \int_0^1 E\{p(t)\} f(p) dp, \quad (\text{A1})$$

where

$$f(p) \approx C p^{2\beta-1} q^{2\beta-1} \exp[-2\alpha\gamma\Delta\tilde{c}_1 p - \alpha\gamma^2 p q]$$

and

$$C^{-1} \approx \int_0^1 p^{2\beta-1} q^{2\beta-1} \exp[-2\alpha\gamma\Delta\tilde{c}_1 p - \alpha\gamma^2 p q] dp.$$

To obtain an explicit formula for $\bar{p}(t)$ we expand the exponential functions in $f(p)$ up to the linear term. Numerical integration with the exponential and linearized versions of $f(p)$ leads to virtually identical results for the parameter values of the main text. For instance, we find for the integrals containing the exponential function $\bar{p}(0) = 0.517$ and for the linearized version $\bar{p}(0) = 0.516$ for $N = 2 \times 10^4$ and the other parameter values given before Equation (24).

Using Equation (23) and the linearized version of $f(p)$, we obtain $\bar{p}(t)$ as

$$\begin{aligned} \bar{p}(t) \approx C^{-1} [& B(2\beta + 1, 2\beta) - 2\alpha\gamma\Delta\tilde{c}_1 B(2\beta + 2, 2\beta) - \alpha\gamma^2 B(2\beta + 2, 2\beta + 1) \\ & - s\gamma\Delta c_1(0)t(B(2\beta + 1, 2\beta + 1) - 2\alpha\gamma\Delta\tilde{c}_1 B(2\beta + 2, 2\beta + 1) - \alpha\gamma^2 B(2\beta + 2, 2\beta + 2))], \end{aligned} \quad (\text{A2})$$

where

$$C^{-1} \approx B(2\beta, 2\beta) - 2\alpha\gamma\Delta\tilde{c}_1 B(2\beta + 1, 2\beta) - \alpha\gamma^2 B(2\beta + 1, 2\beta + 1) \quad (\text{A3})$$

and B is Euler's beta function.

Appendix A.2. Derivation of an Equation for $\hat{p}(t)$

We start from the same formula as in Equation (A1). However, the integral is taken over the interval $[0, p_0]$ instead $[0, 1]$ and C^{-1} is also calculated for this interval, where $p_0 \ll 1$. Furthermore, we linearize the exponential functions and use the approximation $q \approx 1$. This leads to

$$\hat{p}(t) \approx C^{-1} \left[\frac{p_0^{2\beta+1}}{2\beta+1} - (2\alpha\gamma\Delta\tilde{c}_1 + \alpha\gamma^2) \frac{p_0^{2\beta+2}}{2\beta+2} \right] (1 - s\gamma\Delta c_1(0)t), \quad (\text{A4})$$

where

$$C^{-1} \approx \frac{p_0^{2\beta}}{2\beta} - (2\alpha\gamma\Delta\tilde{c}_1 + \alpha\gamma^2) \frac{p_0^{2\beta+1}}{2\beta+1}.$$

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