Focus Article

Polygenic adaptation in changing environments(a)

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Abstract – Although many phenotypic traits are determined by a large number of genetic variants, how a polygenic trait adapts in response to the changes in the environment is still poorly understood. Here we study the adaptation dynamics of a polygenic trait that is determined by a finite number of genetic loci in an infinitely large population which is evolving under stabilising selection and recurrent mutations. We find that in a changing environment, modeled here by a linearly moving phenotypic optimum, the mean trait also moves linearly with time. But its speed is smaller than that of the phenotypic optimum when the effect sizes of the genetic variants are small and approaches that of the environmental change for larger effect sizes. Our study thus highlights the influence of the genetic architecture of a polygenic trait on its adaptability.

Introduction. – Understanding phenotypic variation in terms of the underlying genetic variation is one of the central problems in biological evolution [1]. During the last decade, genome-wide association studies (GWAS) [2] have provided valuable insights into the genetic architecture of phenotypic traits, and the information about the number of genetic variants that affect a phenotype, the size of their effects and their relative frequency is becoming increasingly available [3]. In some cases such as industrial melanism in peppered moth [4], a phenotypic trait is determined by one or few genes. But many phenotypic traits ranging from crop yield and human height to complex diseases are polygenic as they are influenced by a large number of genetic variants. It has been suggested that such quantitative traits may even be omnigenic, determined by all the genes due to the interconnectedness of gene networks [5,6]. The effect sizes of these genetic variants may be large or small, and the proportions in which they occur in a trait is governed by evolutionary forces such as selection [3].

For several decades, the infinitesimal model [7,8] has served as workhorse for describing polygenic adaptation [9]. In this model, an infinite number of genetic loci each with an infinitesimal effect underlie a phenotypic trait. More precisely, the effect size is assumed to decrease with increasing number of loci which results in a genetic variance that remains constant in time in accordance with some phenotypic data [10] and renders the problem analytically tractable. However, the effect sizes can be finite, and genetic variance can change, at least, over some time scales.

Recently a model of polygenic adaptation was introduced [11] in which the phenotypic trait evolves under the action of stabilising selection and mutations. A large but finite number of loci contribute to the trait, and the effect sizes which may be large or small are different at different loci. It is important to note that in [11], an effect size is large or small relative to a scaled mutation rate (defined later) and, unlike in the infinitesimal model, it does not depend on the number of loci under selection.

In this article, we study the adaptation dynamics within the framework of the model in [11] when the phenotypic optimum moves due to a change in the environment. The scenario in which the phenotypic optimum shifts suddenly because of, say, a natural disaster was recently studied and an analytical method was developed to take the changes in the genetic variance into account [12,13]; here we consider the case in which the phenotypic optimum moves gradually as a result of, for example, climate or societal change [14]. Adaptation in the face of moving phenotypic optimum has been previously investigated within
infinitesimal model-ignoring mutations and changes in the genetic variance [15,16]. Here we find that the adaptation dynamics are strongly affected by mutations and the number of loci under selection when the effect sizes are small, and mediated by large transient changes in the genetic variance when the effect sizes are large.

**Models.** We study the evolution of a single quantitative trait in an infinitely large population of diploids. The phenotypic trait value \(z\) is determined by \(\ell\) diallelic genetic loci, each of which contributes to the phenotype in an additive fashion. If the \(\pm\) allele at the \(i\)-th locus has an effect \(\pm \gamma_i/2\) on the trait, the mean phenotypic trait averaged over the population can be written as

\[ c_1 = 2 \sum_{i=1}^{\ell} \left( \frac{\gamma_i}{2} \right) p_i + \left( -\frac{\gamma_i}{2} \right) q_i, \tag{1} \]

where \(p_i\) and \(q_i = 1 - p_i\), respectively, denote the frequency of the \(+\) and \(-\) alleles at the \(i\)-th locus in the population. In the following, the effect sizes are chosen independently from an exponential distribution with mean \(\bar{\gamma}\), as suggested by quantitative-genetic studies [17].

We consider the situation when the allele frequencies and phenotypic properties evolve due to stabilising selection and recurrent mutations. The fitness of a phenotypic trait under stabilising selection is maximum at an optimum phenotypic value \(z_f\) which, in general, may vary with time (see below); away from the optimum, the fitness decreases quadratically, \(w(z) = 1 - (s/2)(z - z_f)^2\), where \(0 < s < 1\) is the strength of selection. Mutations generate variation and here, the \(+\) and \(-\) alleles mutate to each other at rate \(\mu\). We also assume that recombination occurs faster than selection and, therefore, the inter-loci correlations can be ignored (linkage equilibrium) [18]. Then it can be shown that the allele frequency \(p_i\) evolves according to [11]

\[ \dot{p}_i = -s\gamma_i(c_1 - z_f)p_iq_i - \frac{s\gamma_i^2}{2} p_iq_i(q_i - p_i) + \mu(q_i - p_i), \tag{2} \]

where the dot denotes the derivative with respect to time. In the above equation, the first term on the right-hand side (RHS) that depends on the frequency of all the loci acts to decrease the deviation between the mean trait and the phenotypic optimum, the second term tends to fix one of the alleles thus depleting the genetic variation while the third term compensates for the loss in diversity through mutations.

In the stationary state where \(\dot{p}_i = 0\), if the deviation between the mean trait and phenotypic optimum is zero, the stable solutions for the equilibrium allele frequencies are given by [11]

\[ p_i^* = \begin{cases} 1/2, & \gamma_i < \bar{\gamma}, \\ 1/2 \pm 1/2 \sqrt{1 - \frac{\gamma_i^2}{\bar{\gamma}^2}}, & \gamma_i > \bar{\gamma}, \end{cases} \]

where \(\bar{\gamma} = \sqrt{8\mu/s}\). Thus, when the effect size is smaller than the threshold effect \(\bar{\gamma}\), both the alleles are present in the population, whereas for larger effect sizes, one of the alleles is close to fixation. The steady-state deviation in the mean trait from its optimum need not be zero and can be estimated by approximating the effect size of all the loci by the average effect \(\bar{\gamma}\). From (2) in the steady state, we then find the mean equilibrium trait to be \(c_1^*/z_f \approx [1 + 4\mu(8\bar{\gamma}^2)^{-1}]-1\).

In this article, we are interested in the dynamics of the mean trait when the phenotypic optimum moves to a new value. From (2) for the allele frequency, it can be shown that the time evolution equation for the mean trait depends on the variance and skewness of the phenotypic trait and, in general, the dynamics of a trait cumulant depend on two higher cumulants [19]. This cumulant hierarchy makes it difficult to obtain analytical results for the dynamics. However, recent work [12,20] has established that the bulk of the adaptation process is driven by the deviation between the mean trait and the phenotypic optimum. Thus, at short times, it is a good approximation to retain only the first term on the RHS of (2); this yields the directional selection model in which [12]

\[ \dot{p}_i \approx -s\gamma_i(c_1 - z_f)p_iq_i, \quad i = 1, \ldots, \ell. \tag{4} \]

The above equation shows that the mean trait evolves as

\[ \dot{c}_1 = -sc_2(c_1 - z_f), \tag{5} \]

where the genetic variance \(c_2 = 2\sum_{i=1}^{\ell} \gamma_i^2 p_iq_i\). If the genetic variance in (5) remains constant in time, we arrive at Lande’s equation for the evolution of the mean trait [21] which is obviously solvable. But even for time-dependent \(c_2\) and other trait cumulants, the directional selection model is analytically tractable as briefly described below [12]. We first note that for any two loci \(k\) and \(j\),

\[ \frac{dp_j}{\gamma_j p_jq_j} = \frac{dp_k}{\gamma_k p_kq_k} = -s(c_1 - z_f)dt. \tag{6} \]

From the first equality, we find that the allele frequency at the \(j\)-th locus can be expressed in terms of its initial frequency and that at the \(k\)-th locus,

\[ p_j(t) = 1 - \frac{1}{1 + \frac{p_j(0)}{q_j(0)} \left( \frac{\gamma_j}{\beta_j} \right)^{\gamma_j/\beta_j}}. \tag{7} \]

Using this in (1), one can write the mean phenotypic trait as

\[ c_1 = \sum_{i=1}^{\ell} \gamma_i - \sum_{i=1}^{\ell} \frac{2\gamma_i}{1 + \frac{p_i(0)}{q_i(0)} e^{\beta_i/\gamma_i}}, \tag{8} \]

where

\[ \beta(t) = \frac{\bar{\gamma}}{\bar{\gamma}_k} \ln \left( \frac{p_k(t)q_k(t)}{p_k(0)q_k(0)} \right), \tag{9} \]

is locus-independent and, due to (4), evolves as

\[ \dot{\beta} = -s\bar{\gamma}(c_1 - z_f). \tag{10} \]

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Equations (8) and (10) together yield a closed equation for the mean trait.

Results. — We start with a population equilibrated to the phenotypic optimum at \( z_0 \). The phenotypic optimum moves linearly until a time \( \tau \) when it reaches \( z_\tau > z_0 \) where it stays for later times. Thus, the new phenotypic optimum \( z_f(t) = z_0 + vt, t < \tau \), where the velocity \( v = (z_\tau - z_0)/\tau \). Here, \( |z_0|, |z_\tau| < \ell \gamma \) as the mean trait is bounded for finite \( \ell \). Our goal is to understand how the population adapts while the environment is changing. In the following, all the numerical data are obtained for a single realisation of effects as the quantities of interest are expected to be self-averaging [12].

When most effects are small (\( \gamma \ll \bar{\gamma} \)). Figure 1 shows that for linearly moving phenotypic optimum, the mean trait also increases linearly with time at a speed that decreases as the number of loci determining a trait decreases. However, the genetic variance \( c_2 \) (shown in the inset) remains close to its stationary value \( c_2^* \approx \ell \gamma^2 \) [11] until time \( \tau \) and then decreases to the stationary genetic variance corresponding to the equilibrium mean trait \( c_1^* \) [12]. For the parameters in fig. 1, we expect \( c_1^*/z_\tau \) to be 0.24, 0.39, 0.56 (see the discussion following (3)) which is close to \( c_1(\tau)/z_\tau = 0.33, 0.47, 0.62 \) for \( \ell = 50, 100, 200 \), respectively. For this reason, the mean trait does not change substantially when the phenotypic optimum stops moving.

For \( t \ll \tau \) where the genetic variance is approximately constant, (5) for the evolution of the mean trait simplifies to \( c_1(t) \approx sc_2^*(z_f(t) - c_1(t)) \) which can be readily integrated to yield

\[
c_1(t) = z_0 + vt - \frac{v}{sc_2^*}(1 - e^{-sc_2^*t}), \quad t < \tau, \tag{11}
\]

and shows that the mean trait always lags behind the moving phenotypic optimum. At short times (\( \ll (sc_2^*)^{-1} \)), the mean trait increases quadratically. But at longer times, \( c_1 \) increases linearly with speed \( v \) and the lag \( z_f(t) - c_1(v, t) \) reaches a constant value \( v/(sc_2^*) \). This result has also been obtained in the infinitesimal model [15,16] in which an infinite number of loci, each with an infinitesimal effect (\( \sim \ell^{-1/2} \)), contribute to a phenotypic trait and the mean trait keeps increasing in an unbounded fashion; here, as a finite number of loci contribute to the trait, the linear behaviour of the mean trait sets in at a time \( \sim \ell^{-1} \) and continues until the time \( \tau \).

Figure 2 shows that for \( (sc_2^*)^{-1} \ll t \ll \tau \), the lag is constant in the directional selection model and matches the prediction (11) but it keeps increasing linearly with time in the full model. To understand this behaviour, we note that at short times, by virtue of (3), the allele frequencies are close to one half and, therefore, the last two terms on the RHS of (2) can be ignored [12]. Indeed, as fig. 2 shows, the full model and the directional model are in good agreement at short times. But at longer times, the allele frequencies are not in equilibrium and for \( z_\tau > z_0 \), as is assumed here, the frequency of the + allele increases towards one. Moreover, when the effects are small, the mutation rate is large (\( \mu > sc_2^*/8 \)). These considerations suggest to modify the directional selection model (4) by adding the mutation term to it when the phenotypic optimum is moving. The mean trait then evolves according to

\[
c_1(t) \approx sc_2^*(z_f(t) - c_1(t)) - 2\mu c_1(t), \tag{12}
\]

which shows that at large times, the mean trait increases linearly as \( c_1(t) = ut + \lambda \), \( (sc_2^* + 2\mu)^{-1} < t < \tau \), where

\[
u = \frac{v}{1+2\mu(sc_2^*)^{-1}}, \quad \lambda = \frac{z_0 - u(sc_2^*)^{-1}}{1+2\mu(sc_2^*)^{-1}}. \tag{13}
\]

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The inset of fig. 2 shows that the rate of change of the mean trait is in agreement with the speed $\alpha$.

Equation (13) above makes two important points. First, the mean trait in the full model (2) increases slower than the phenotypic optimum with increasing mutation rates. At short times where the allele frequencies are close to their equilibrium value given by one half, mutations occurring at equal rate between the + and − alleles do not affect the dynamics. But at larger times, as the + alleles become more abundant than the − alleles owing to selection, the net effect of the mutations is deleterious leading to an increased lag in the mean trait. Second, the speed of the mean trait increases with the number of loci under selection. When $\gamma$, $\tilde{\gamma}$ are of order one (as is the case here), mutation is weaker than selection and may be neglected when $\ell \to \infty$. But for a finite number of loci, mutations also enter the picture and, as argued above, decrease the speed of the mean trait.

When most effects are large ($\tilde{\gamma} \gg \gamma$). Since the mutations are unimportant when effect sizes are large, the directional selection model (4) describes the full model well (see figs. 3 and 4). The inset of fig. 3 shows that the genetic variance remains close to its equilibrium value $\sigma^2 = \ell \tilde{\gamma}^2$ [11] for some time, rises quickly to $\tilde{c}_2 \sim 100 \sigma^2$ where it stays before finally dropping to $c_2$. As $\sigma^2$ is very small for the parameters in fig. 3, due to (5), the mean trait remains close to $z_0$ initially and then increases before saturating to $c_1^{\beta} \approx z_\gamma$. Since the genetic variance changes during the time intervals of interest, (5) for the mean trait evolution does not close and, therefore, we now work with (8) and (10).

As the equilibria are bistable for large effects (see (3)), a fraction $f$ of the initial population carries the + allele which is related to the initial phenotypic mean through $z_0 \approx (2f - 1)\tilde{\gamma}$. We may therefore write the mean trait (8) as

$$c_1 = \sum_{i=1}^{\ell} \left( \gamma_i - \frac{2\gamma f}{1 + \hat{\gamma}_i} - \frac{2\gamma_i (1 - f)}{1 + \hat{\gamma}_i} \right), \quad (15)$$

which, for large $\ell$, simplifies to

$$\frac{c_1(t)}{\tilde{\gamma}} \approx 1 - \left( 1 + \frac{z_0}{\tilde{\gamma}} \right) I_+ (\beta) - \left( 1 - \frac{z_0}{\tilde{\gamma}} \right) I_- (\beta), \quad (16)$$

where

$$I_{\pm} (\beta) = \int_{1/a}^{\infty} \frac{x e^{-x}}{1 + (ax)^2 e^{\beta x}} \quad (17)$$

and $\alpha = 2\gamma/\tilde{\gamma} \gg 1$. Equation (16) generalises eq. (24) of [12] where the initial phenotypic optimum is taken to be zero.

We first note that $\hat{\beta}, \beta \geq 0$ — the first assertion follows from the intuitive expectation that the lag must always be non-negative and (10), and the second one on using $\beta(0) = 0$ (see (9)). Then it is easy to see that for large $\alpha$, the integral $I_+ \to 0, I_- \to 1$. Neglecting $I_+$ in (16) and writing $I_- = \int_{1/a}^{\infty} \frac{x e^{-x}}{1 + (ax)^2 e^{\beta x}} \approx 1 - J_-$, we find that the parameter $\beta$ evolves according to

$$\ddot{\beta} = s \tilde{\gamma} (\ell \tilde{\gamma} - z_0) \left[ \rho(t) - J_- (\beta) \right], \quad (18)$$

where

$$J_- = \int_{2/a}^{\infty} \frac{x e^{-x}}{1 + (ax)^2 e^{\beta x}} \quad (19)$$

and $\rho(t) = vt/(\ell \tilde{\gamma} - z_0)$. For $\beta \ll 1$, the integral $J_- \approx 0$ as it is heavily suppressed by the factor $\alpha^2$ in the denominator of the integrand [12]. For $\beta \gg 1$, the integral $J_-$ may be estimated by approximating the factor $(1 + (ax)^2 e^{\beta x})^{-1}$ in the integrand of $J_-$ by a Heaviside theta function $\Theta(x - x_-)$ where $x_- (\beta)$ is a solution of $\alpha^2 x^2 e^{-\beta x} = 1$. We thus obtain $J_- \approx (1 + x_-) e^{-x_-}$, $\beta \gg 1$ [12].
We are now in a position to understand the behaviour of the mean trait given by

\[ c_1(t) - z_0 = (\ell \gamma - z_0) J_-(\beta) = \nu t - \frac{\dot{\beta}}{s\gamma}, \tag{20} \]

where we have used (18) to express \( J_- \) in terms of \( \dot{\beta} \).

At short times \( t < t_0 \), as the mean stays close to its initial value \( z_0 \), the integral \( J_- \approx 0 \) and, therefore, \( \beta(t) = (t/t_0)^2 \), where \( t_0 = \sqrt{2/(s\gamma)} \). After time \( t_0 \), there is a large increase in the genetic variance and the mean trait starts evolving. Note that if the genetic variance was held constant at its initial value, as in the infinitesimal model, the mean trait will stay at \( z_0 \) and the population cannot adapt.

In the time interval \( (s\ell^2)^{-1} < t < \tau \) where the mean trait increases linearly, the genetic variance \( \tilde{c}_2 \gg \ell^2 \) remains roughly constant. To estimate \( \tilde{c}_2 \), we note from the inset of fig. 4 that the allele frequencies at loci with effect size larger than \( \gamma \) sweep to fixation much earlier than at loci with smaller effect sizes. For the set of effects used in fig. 4, the allele frequencies at 3 loci with effect size \( \approx 0.4 \) swept to fixation while nearly 30 selective sweeps occurred when the optimum was shifted suddenly to \( z_\tau \) (data not shown). Large changes in allele frequency at many loci in the latter case are consistent with the fact that the population adapts exponentially fast over a short time scale (that decreases with \( \ell \)) when the optimum shifts suddenly [12]; here the mean deviation changes slowly over a time of order \( \ell \) and besides a few sweeps, many small frequency shifts (\( \approx 0.1 \)) also occur. While the selective sweep is in progress at loci with very large effects, the genetic variance rises to \( \tilde{c}_2 \sim \ell \int_{\gamma}^{\infty} d\gamma \gamma^2 p(\gamma) \sim \ell \gamma^2 \). Then replacing \( \ell^2 \) by \( \tilde{c}_2 \) in (13) and using that \( \bar{\gamma} \ll \gamma \) when effects are large, it follows that, in the infinitesimal model, the mean trait increases with speed \( \nu \) and lag \( \nu/s(\tilde{c}_2) \).

We now perform a more careful analysis of the lag in the mean. The above discussion shows that the lag \( \dot{\beta}/s\bar{\gamma} \) (second equality in (20)) is small for \( \ell \gg 1 \). Therefore, to a first approximation, we may write \( \rho(t) \approx J_-(\beta) \) in (18) which yields

\[ x_-(t) = -1 - W_{-1} \left( -\frac{\rho(t)}{e} \right), \tag{21} \]

where \( W_{-1}(x) \) is the lower branch of the Lambert W function [22]. Using \( \beta = (2/x_-) \ln(\alpha x_-) \), we find that

\[ \dot{\beta} = \frac{2}{t} \frac{W_{-1}(-\rho/e)}{[1 + W_{-1}(-\rho/e)]^3} \ln \left( \frac{1 + W_{-1}(-\rho/e)}{-\rho/e} \right). \tag{22} \]

For \( t \ll \tau \) where \( \rho/e \ll 1 \), the function \( W_{-1}(-\rho/e) \approx \ln(\rho/e) \sim \ln t \) [22] so that \( \dot{\beta} \sim t^{-1} \). Thus, when most effects are large, the mean trait moves with speed \( \nu \) but the lag between the mean trait and phenotypic optimum is not a constant. Although the lag \( \approx (s\gamma^2 t)^{-1} \) decays rapidly with time, it is larger than that obtained within the infinitesimal model for a polymorphic population since the above discussion is valid for \( t < \tau \), see fig. 4. Furthermore, (5) and (10) show that the genetic variance \( \bar{c}_2(t) = (sw\gamma - \beta)/(s^2\gamma^2 z_0 + \beta) \) which on using the above results for \( \beta \) yields \( \bar{c}_2(t) \sim \nu \gamma t \). Thus, on time scales of order \( \tau \), we obtain the genetic variance to be \( \bar{c}_2 \) in agreement with the argument above. Since the genetic variance increases from \( \bar{c}_2 \) to \( \bar{c}_2 \), for fixed \( \gamma_1, \gamma_2 \), a large change in variance occurs with increasing \( \ell \). But the change in variance is smaller if the mean effect and the threshold effect are not substantially different (see fig. 5).

**Summary and open questions.** – While stabilising selection has the tendency to pull the population towards the phenotypic optimum, recurrent mutations create variants that push the population away from it. The behaviour of the mean trait in the large-effects case where selection is the dominant process resembles that in the infinitesimal model as the mean trait moves with the speed of the phenotypic optimum, while in the small-effects case in which mutation rates are large, the mean trait moves slower than the phenotypic optimum. However, in the latter case, as the number of genetic loci affecting a trait increases, selection dominates over mutations and the speed of the mean trait approaches that of the phenotypic optimum (also, see the discussion after (14)).

In the large-effects case as the initial variance is small, the mean trait stays close to its initial value resulting in large deviation from the moving phenotypic optimum. But this causes the allele frequencies to change in a manner that increases the genetic variance thus paving the way for adaptation. On the other hand, when most effects are small, there is sufficient initial genetic variance for adaptation to proceed keeping genetic variance constant.

In the last section, we studied two limiting cases of the genetic architecture, viz., when \( \gamma/\bar{\gamma} \) is much smaller or larger than unity. Figure 5 shows that when both small
and large effect sizes constitute a phenotypic trait, the behaviour of the mean trait is closer to the mostly large-effects case, possibly because the contribution of the small effect sizes to the mean trait increases slower than that of the large-effects loci. Thus, we conclude that, in general, the lag between mean trait and phenotypic optimum exceeds that predicted by the infinitesimal model for a polymorphic population [15,16].

Although the study presented here goes beyond the standard quantitative-genetic theory [15,16] by accounting for mutations and temporal changes in genetic variance, this work also has some limitations—we have neglected the effect of epistasis in the genotype-phenotype map, pleiotropic effects of other phenotypic traits and, perhaps most importantly, the finiteness of the population size. The effect of stochastic fluctuations on the speed of adaptation and extinction risk has been addressed in recent work [23,24] when the genetic variance remains constant. Extending the results presented here to finite populations is desirable and we plan to address this in a future work.

**References**

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