universität wien

DISSERTATION

Titel der Dissertation

The genetics of adaptation in changing environments

Verfasser

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angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr. rer. nat.)

Wien, im November 2014

Studienkennzahl lt. Studienblatt:	A 791 405
Dissertationsgebiet lt. Studienblatt:	Mathematik
Betreuer:	Univ.-Prof. Dr. Joachim Hermisson
	Univ.-Prof. Dr. Michael Kopp

Danksagung

"Ich denke niemals an die Zukunft. Sie kommt früh genug."

— Albert Einstein

Sowohl in persönlicher als auch in wissenschaftlicher Hinsicht waren die vergangen vier Jahre für mich vom Thema "Anpassung an sich verändernde Umwelten" geprägt. Ich möchte mich an dieser Stelle daher bei allen Personen bedanken, die mich bei diesem Prozess begleitet und unterstützt haben, die mich permanent angetrieben und ermutigt haben, mich und diese Arbeit zu verbessern. Wie bei den in Kapitel 2 dieser Arbeit betrachteten "Adaptive walks" war dieser Weg – wie auch das Leben selbst – nicht immer linear[1]. Vieles von dem was ich seinerzeit als "deleterious mutation" betrachtet habe, sehe ich heute zurückblickend positiv. Vielmehr bin ich heute dankbar für diese "pleiotropen Nebeneffekte" und begreife jene nun als Chance, mich in anderen Bereichen weiterzuentwickeln.

In diesem Sinne möchte ich mich bei Prof. Michael Kopp bedanken, dass er mich nach Wien brachte und mir die Möglichkeit und das Vertrauen gab, in diesem, zum damaligen Zeitpunkt mir wenig vetrauten, Forschungsgebiet, meine Doktorarbeit anzufertigen. Danke auch für die wertvolle und unbeschreibliche Auslandserfahrung in Marseille sowie die Geduld und Ausdauer in den vielen und langen Skypekonferenzen. Darüber hinaus möchte ich mich bei Prof. Joachim Hermisson für seine uneingeschränkte Unterstützung und Förderung sowohl auf fachlicher als auch persönlicher Ebene bedanken.

Für viele weitere unvergessliche Erlebnisse und die außerordentliche Unterstützung während der letzten Jahre möchte ich mich außerdem, wenn auch nicht so ausführlich, aber dennoch namentlich bedanken bei (alphabetisch geordnet): Andrea Betancourt, Alexandre Blanckaert, Jon Bollback, Claudia Brunner, Reinhard Bürger, Jérémie Chalopin, Pauline Charruau-Dau, Luis-Miguel Chevin, Dreh&Trink Ultimate Vienna, Jane and Greg Ewing, Cécile Fleur, Andrea Fulgione, Ludwig Geroldinger, Angela Hancock, Ines Hellmann, Josef Hofbauer, Aurica Höhne, Ilse Höllinger, Christian Huber, Christoph Krall, Anne Kupczok, Konrad-Lorentz Institut für Evolutions- und Kognitionsforschung,

[1] Andreas Zachhuber, deutscher Fußballlehrer: "Das Leben ist eine Sinuskurve". Schon damals als Mathematikstudent wie auch heute entlockt mir diese Lebensweisheit ein Lächeln.

Les Marsiens, Christopher Mann, Sylvain Mousset, Sebastian Novak, Mihaela Pavličev, Jitka Polechova, Agnes Rettelbach, Christin Ruchay, Claus Rüffler, Kristan Schneider, Derek Setter, Hannes Svardal, Ada Temme, Hildegard Uecker, Claus Vogl und Helene Weigang.

Zu guter Letzt, aber in erster Linie, möchte ich mich bei meiner Familie für die Unterstützung in dieser Zeit und speziell in den letzten Monaten bedanken. Das sind meine Großeltern Ingrid und Arno, meine Eltern Heike und Fridjof, meine Schwiegereltern (in spe) Gudrun und Jürgen und natürlich meine Freundin Janett – ohne Dich wären die letzten Jahre nicht halb so schön gewesen.

In diesem Sinne möchte ich diese Danksagung mit dem zu Beginn angeführten Zitat in leicht abgewandelter Form schließen.

Ich denke niemals an die Zukunft. Sie kommt früh genug. Aber ich freue mich darauf.

Preface

This thesis comprises of my research in the field of mathematical population genetics that I have carried out during my doctoral studies at the University of Vienna in the past four years. The manuscript is structured into three parts, each corresponding to a published or (soon to be) submitted paper.

All three chapters of the following work are connected by the overriding question of my research, i.e., how do populations adapt in the face of changing environmental conditions? And more specifically, how does a population's ability to respond to environmental change and the characteristics of the adaptive process depend on the general forces of evolution, i.e., selection, mutation and recombination, and ecological factors, such as the mode and tempo of environmental change?

In the first part, *Rapid evolution of quantitative traits: theoretical perspectives*, we review theoretical models of rapid evolution in quantitative traits. Special focus is put on the implications and limits of maximal sustainable rates of genetically-based change and their adequacy for assessing the risk of population extinction in changing environments.

In the second part, *Fisher's geometric model with a moving optimum*, we study adaptation of multiple pleiotropically related traits to a moving selective optimum, which allows us to capture both the dynamic nature of selection pressures and the complexity and high-dimensionality of organismic phenotypes. This marks an important step towards more realistic models of adaptation, as it integrates two modelling traditions which have had little overlap so far: on the one hand, the multivariate moving-optimum model as used by Jones et al. (2004, 2012), and on the other hand, Fisher's classical geometric model of adaptation (Fisher 1930; Orr 1998, 2000).

Finally, in the third part, *Catch me if you can: On the importance of standing genetic variation for the genetics of adaptation in changing environments*, we aim to contribute to overcoming what has been described as "the most obvious theoretical limitation when describing the adaptive process" (Orr 2005b), that is the description of the ecological and genetic factors that determine the genetic basis of adaptation from standing genetic

variation. Specifically, we consider the evolution of a quantitative trait to a gradually changing environment. By means of analytical approximations, we derive the distribution of standing adaptive substitutions, that is, the distribution of the phenotypic effects of those alleles that become fixed during adaptation and which originated from standing genetic variation.

A more detailed motivation and discussion of these scenarios, with respect to implications for current and future research, their necessary simplifications and limitations, and their interrelatedness is given in the subsequent introduction.

Finally, in accordance with the formal criteria for cumulative dissertations, each paper is followed by a separate paragraph that contains information about the status of submission (as of November 2014) and my personal contribution. For the ease of readability, each paper has its own bibliography. An overall bibliography for all chapters including the preamble and the synopsis is given at the end of this thesis.

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Preamble

> "As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be naturally selected. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form."
>
> — Charles Darwin, *The Origin of Species*

Adaptation lies at the heart of Darwinian evolution. To avoid extinction, natural populations must adapt to frequent changes in their environment. This issue is particular pressing in the context of global climate change, which subjects large numbers of populations to shifts in temperature, aridity, seasonal patterns etc. While this human-induced global environmental change has driven many populations close to extinction, others have managed to respond to the altered conditions. Since 1975, 12% of the local Mexican *Sceloporus* lizard populations have gone extinct, as the heliothermal reptile was not able to adapt its thermal physiology to the rising temperatures, with physiological models of extinction risk predicting that 39% of these populations will be lost by 2080 (Sinervo et al. 2010). On the contrary, Darwin's finches that faced an extreme drought in 2004 causing 85% of the population on Daphne island to die, were able to adapt their beaks to other food resources and, thus, managed to survive (Grant and Grant 2006). As the number of empirical studies of adaptation to changing environments continue to pile up, theory – until recently – has lacked behind considerably. Consequently, the answers to seemingly simple questions are unknown even for simple scenarios. This includes questions such as: from the set of mutations that emerge in a population, which are the ones that will get fixed, and what is their effect on phenotype or fitness? Can we predict which populations have the potential to adapt to rapid climate change, and how and when do genetic and ecological factors constrain or facilitate adaptation? What is the relative role of standing genetic variation (i.e., alleles that are already present in the population) versus new mutations during short- and medium-term adaptation, and how do the characteristics of adaptation differ between these? The main question of this thesis is, thus,

put very generally: How do populations adapt to changing environments? Special focus is, furthermore, laid on the interplay of the evolutionary forces such as selection, mutation and recombination, and ecological factors – i.e., mode and tempo of environmental change – and their joint effects for the genetics of adaptation.

In recent years several studies have tried to provide a formal framework for the description of the adaptive process. Many of these are built on two complementary modelling approaches. The first approach focuses on the statistical properties of adaptive substitutions (i.e., beneficial mutations that thrive to fixation) as opposed to the dynamics of genotypes or allele frequencies. Many models are either based on Fisher's geometric model (Fisher 1930; Orr 1998, 2000; Martin and Lenormand 2006a) or so-called adaptive-walk or mutational landscape models (Gillespie 1984; Kauffman and Levin 1987; Orr 2002), and they usually consider the simplest possible scenario of environmental change, i.e., a population evolving towards a constant phenotypic optimum after a sudden shift in the environment. Remarkably, despite its simplicity and the lack of a clear genetic context (Chevin et al. 2010b), Fisher's geometric model, more than 80 years after its proposal, has yielded several robust predictions supported by growing empirical evidence (Martin and Lenormand 2006a,b, 2008). An important aspect of these models is the assumption that selection is strong compared to mutation so that the population can be considered monomorphic all the time and that all observed evolutionary change is the result of new mutations.

In stark contrast, quantitative-genetic models consider an inexhaustible pool of preexisting standing genetic variants as the sole source for adaptation. Evolving traits are assumed to have a polygenic basis where many loci contribute small individual effects, such that the distribution of trait values follows approximately a Gaussian distribution (Bulmer 1980; Barton and Turelli 1991; Kirkpatrick et al. 2002). For historical reasons, however – quantitative-genetic models were intended for and have ever since successfully been used to design plant and animal breeding schemes (Wricke and Weber 1986; Tobin et al. 2006; Hallauer et al. 2010) –, the focus of these models was on predicting short-term changes in the population mean phenotype $\bar{z}$ instead of following allele frequency changes at individual loci. Furthermore, the change in the population mean phenotype $\Delta\bar{z}$ after one generation of selection can easily be projected by the key theoretical tool for studying phenotypic evolution, that is, the Lande equation (Lande 1976a)

$$\Delta\bar{z} = \sigma_g^2\beta, \tag{1.1}$$

where σ_g^2 is the additive genetic variance and β denotes the selection gradient, i.e. the regression of fitness on phenotype. Repeated application of the Lande equation, however, presupposes that the distributions of genotypes and phenotypes remain Gaussian and that σ_g^2 remains constant. While this might be approximately true for short-term evolution, over longer timescales – in particular, when studying adaptation to prolonged environmental change – σ_g^2 is itself subject to evolutionary change and strongly depends on the input of new mutations.

Thus, to foster our understanding on how populations adapt to environmental conditions we need to construct a theory of adaptive evolution "that speaks in the same terms as the data; that is in terms of individual mutations that have individual effects" (Orr 2005a); these data critically involve new mutations and standing genetic variation. Thus, bridging the gap between adaptive-walk and quantitative-genetic models – the two extremes of a continuum of adaptive approaches – is a necessary and important step towards a general theory of adaptation.

Another aspect that has been largely ignored until recently, is that adaptation ultimately occurs as an evolutionary response to environmental change – a process that is itself inherently dynamic. While the vast majority of studies have focused on the simplest possible scenario, i.e., a single sudden shift in the environment, already Maynard Smith (1976) pointed out the necessity to include gradual environmental change into studies of adaptive evolution. Collins (2011a) recently emphasized that "using [models] of instantaneous environmental change to understand adaptive evolutionary responses to gradual change will not only underestimate the amount of adaptation, but also predict the wrong genotypic and phenotypic changes."

This discrepancy becomes particularly acute when put into the context of conservation biology. While the past two decades have made it clear that evolutionary change can be fast enough to be observed in present-day populations (Hendry and Kinnison 1999; Collins et al. 2007; Lindsey et al. 2013), one of the key questions is, whether or not it is fast enough for populations to keep track with the altering environmental conditions. Thus, identifying those populations that are threatened by extinction and require targeted conservation programs is one of the main challenges in current evolutionary biology – a challenge that would benefit a lot from a more realistic and general theory of adaptation.

The aim of this thesis is thus to study the combined effects of gradual environmental change, standing genetic variation and organismic complexity on the genetic basis of phenotypic adaptation to provide a first step towards a generalized model of adaptation

that reflects both the dynamic nature of selection and the complexity of real organisms, and which allows to make testable predictions for both short- and long-term evolution.

Rapid evolution of quantitative traits: theoretical perspectives.

In the first part (published; see Kopp and Matuszewski 2014), we review theoretical models addressing the potential for adaptation to a changing climate. In particular, we focus on quantitative traits, that is, traits with continuous variation that are determined by a large number of loci with appreciable standing genetic variation, and whose optimum changes gradually over time. Specific emphasis is laid on "critical rates of environmental change" or "maximal sustainable rates of evolution", a concept introduced by Lynch and Lande (1993) and Bürger and Lynch (1995) to calculate rates of environmental (and evolutionary) change beyond which long-term population persistence is not possible. While this concept has subsequently been extended to include multivariate selection (Gomulkiewicz and Houle 2009), spatial variation (Duputié et al. 2012) and phenotypic plasticity (Chevin et al. 2010b), one key result remains valid: Maximal sustainable rates of evolutionary change are on the order of 0.1 *haldanes*, which is equivalent to a per-generation change of 0.1 phenotypic standard deviations in the mean population phenotype. Several meta-analyses of contemporary evolution show, however, that evolutionary rates above 0.1 *haldanes* are not uncommon (Hendry and Kinnison 1999; Gingerich 2009), even though the majority of rates are lower. This observation has led Barrett and Hendry (2012) to criticize theory-derived critical rates, arguing that these rely on many unrealistic assumptions, such as the "perpetual persistence under constant environmental change", and that "critical rates for natural populations over time frames of conservation interest could be very different."

Building on the model of Bürger and Lynch (1995), we attempt to evaluate these claims by calculating critical rates of environmental and phenotypic change that allow the population to remain above a critical size (e.g., 50 individuals) over a time frame of 50 generations. These calculations are, however, based on a deterministic approximation, which neglects various sources of stochasticity. To quantify how rates of phenotypic change are influenced by non-selective factors, such as genetic drift or environmental variance, the deterministic model is further complemented by individual-based simulations. Due to these modifications, we can no longer consider a dynamic equilibrium between environmental and evolutionary change, so that critical rates of environmental change and maximal sustainable rates of evolutionary change are no longer equivalent. Indeed, we find that critical rates of *environmental* change over modest time frames are

substantially higher than those predicted by Bürger and Lynch (1995). In constrast, maximal sustainable rates of *evolutionary change* – the only rates that can be measured in empirical studies – remain largely unaltered, in particular, if the population is allowed only a modest decline. Indeed, the observed differences between maximal evolutionary rates over short and long timescales rarely exceed 30%. Such differences appear minor in relation to the uncertainty in estimates of evolutionary rates that is introduced by stochastic fluctuations. In particular, we show that, in small populations genetic drift alone can induce generation-to-generation rates of change of up to 0.15 *haldanes* (even under constant environmental conditions), thus, largely surpassing the 0.1 *haldanes* predicted by Bürger and Lynch (1995). Overall, these results cast serious doubt on our ability to identify populations facing extinction based on short-term measures of micro-evolutionary change.

Fisher's geometric model with a moving optimum.

In the second part (published; see Matuszewski et al. 2014a), we now shift focus towards what has been phrased "the fundamental event during adaptation" (Kopp and Hermisson 2009b), that is the substitution of a resident allele (i.e., gene variant) by a beneficial mutation. An important goal of current research – both empirical and theoretical – is to learn more about the statistical properties of these substitutions (Orr 2005b). In particular, much effort is being devoted to understanding the distribution of the effects of new mutations (with respect to phenotype and fitness; e.g., Martin and Lenormand 2006b; Eyre-Walker and Keightley 2007; Martin and Lenormand 2008) and the distribution of the subset of those mutations that go to fixation and contribute to adaptation (Gerrish and Lenski 1998; Orr 1998, 2002; Kopp and Hermisson 2009b; Mackay et al. 2009). The main tool for studying the "distribution of adaptive substitutions" has been Fisher's geometric model (FGM; Fisher 1930), which addresses the situation in which a population is confronted with constant stabilizing selection after a sudden environmental change. Under this scenario, FGM has yielded three main predictions, which are supported by growing empirical evidence: First, the distribution of fitness effects of new mutations is well approximated by a (displaced) negative gamma distribution (Martin and Lenormand 2006a; for empirical support see Hietpas et al. 2013). Second, the distribution of adaptive substitutions is approximately exponential, meaning that most fixed mutations are of small and only a few are of large effect (Orr 1998; for empirical support see Rockman 2012, but see Bell 2009). Finally, fixed mutational effects become on average smaller as organismic complexity (i.e., the number of phenotypic traits) increases (Orr 2000; for

empirical support see Cooper et al. 2007) – a phenomenon that has been termed "the cost of complexity" (Orr 2000; Welch and Waxman 2003b; Wagner and Zhang 2011).

In contrast to the classical Fisher model, a number of recent studies has focused on the so-called moving-optimum model, which describes the evolution of a quantitative trait that is under stabilizing selection towards an optimal phenotype that changes over time (Lynch and Lande 1993; Bürger and Lynch 1995; Waxman and Peck 1999; Bürger and Gimelfarb 2002; Nunney 2003; Bello and Waxman 2006). These studies take into account that environmental change in nature might often be gradual than sudden (Thompson 2005; Parmesan 2006; Perron et al. 2008) and meet the long been recognized necessity to include gradual environmental change into studies of adaptive evolution (Maynard Smith 1976). Characteristics of individual substitutions in the moving-optimum model have been investigated by (Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b). These studies showed that selection for a moving optimum produces patterns that are fundamentally different from those predicted under constant selection after a single, abrupt change in the environment. In particular, the distribution of adaptive substitutions is unimodal (with an intermediate mode) rather than exponential, that is, most substitutions have an intermediate phenotypic effect, while small- and large substitutions are rare. Furthermore, this distribution is entirely determined by a scaled rate of evolutionary change, which combines both ecological and genetic factors.

Previous studies of the genetic basis of adaptation in the moving-optimum model, however, only considered the evolution of a single trait (Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b) . While this provided a minimal model for analyzing adaptation in gradually changing environments, selection in nature does not act on single traits, but on entire organisms. Living organisms possess numerous traits, each of which depend on a large number of genes. These genes are physically linked on chromosomes (linkage), they interact with each other in non-linear ways (epistasis), and each gene typically affects several traits at once (pleiotropy). Hence, adaptation takes place in very complex and high-dimensional genotype and phenotype spaces. An obvious question is, hence, how the single-trait results are affected if adaptation to gradually changing environments is constrained by pleiotropic correlations among traits under selection. To answer this question, we add a key feature of FGM to the moving-optimum model, that is the effect of phenotypic complexity (or pleiotropy; which is equivalent in the context of FGM). By means of analytical approximations and individual-based simulations we study how the expected distribution of adaptive steps is influenced by the rate of environmental change, the number of traits under selection (i.e, organismic complexity), and

by selectional and mutational correlations (i.e., the shape of the fitness landscape and the multivariate distribution of new mutations).

Along with previous single-trait studies, our analysis shows that the genetic basis of the adaptive process critically depends on the tempo and mode of environmental change. In particular, we show that the distribution of adaptive substitutions is largely determined by a single composite parameter γ, which scales the rate of environmental change relative to the "adaptive potential" of the population and defines a continuum between environmentally- and genetically-limited adaptation (*sensu* Kopp and Hermisson 2009b). In the environmentally-limited regime (i.e., slow environmental change), the population follows the optimum closely, adaptive steps are small and their multivariate distribution mirrors the shape of the fitness landscape. In the genetically-limited regime (i.e., fast environmental change), in contrast, the population follows the optimum with a large gap, adaptive steps are large and their distribution is determined primarily by the distribution of new mutations. Thus, our results confirm and extend previous studies of adaptive evolution to changing environments for single traits (Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b). Furthermore, the effect size of fixed mutations increases with the degree of pleiotropy (i.e., organismic complexity), in contrast to classical predictions from Fisher's geometric model (FGM) under sudden environmental change. Along the same line, long-term persistence is likely restricted to the environmentally-limited regime – where adaptation proceeds "smoothly" in small steps – but the parameter range for this regime is reduced in complex organisms. In particular, the maximal rate of environmental change (Bürger and Lynch 1995, see above) decreases with organismic complexity.

Catch me if you can: On the importance of standing genetic variation for the genetics of adaptation.

Like the majority of the theory on the genetics of adaptation (Orr 2000, 2005a; Kopp and Hermisson 2009b; Matuszewski et al. 2014a), the second part of this thesis has focused on adaptation from new mutations. As mentioned above, these adaptive-walk models (Gillespie 1984; Kauffman and Levin 1987; Orr 2002, 2005b) have produced robust predictions (Orr 1998, 2000; Martin and Lenormand 2006a) that are supported by empirical data (Cooper et al. 2007; Rockman 2012; Hietpas et al. 2013). The downside to this success, however, is that, with respect to the genetic basis of adaptation "we cannot say anything about adaptation from standing genetic variation" (Orr 2005b). Quantitative-genetic models cannot provide an answer, either, because, while focusing exclusively on standing genetic variation, they do not follow the evolution of individual alleles.

It is only in the past decade that population geneticist have thoroughly addressed adaptation from standing genetic variation at the level of individual substitutions (Orr and Betancourt 2001; Hermisson and Pennings 2005; Chevin and Hospital 2008). Hermisson and Pennings (2005) calculated the probability of adaptation from standing genetic variation following a sudden change in the selection regime. They found that, for small-effect alleles, the fixation probability is considerably increased relative to that from new mutations. Similarly, Chevin and Hospital (2008) showed that the selective dynamics at a focal locus are substantially affected by genetic background variation. Performing experimental evolution in yeast, Lang et al. (2011) followed beneficial mutations in hundreds of populations and showed that the selective advantage of a mutation plays only a limited role in determining its ultimate fate. Instead, fixation or loss is largely determined by variation in the genetic background – which might not be preexisting, but could quickly be generated by a large number of new mutations. Still, predictions for the genetics of adaptation from standing genetic variation have been verbal at best, stating that "compared with new mutations, adaptation from standing genetic variation is likely to lead to faster evolution [and] the fixation of more alleles of small effect [...]" (Barrett and Schluter 2008). Thus, despite recent progress, one of the central questions still remains unanswered: From the multitude of standing genetic variants segregating in a population, which are the ones that ultimately become fixed and contribute to adaptation, and how does their distribution differ from that of *de-novo* mutations?

The aim of the third part of this thesis (in preparation; see Matuszewski et al. 2014b) is to contribute to overcoming what has been described as "the most obvious theoretical limitation when describing the adaptive process" (Orr 2005b) and to study the ecological and genetic factors that determine the genetic basis of adaptation from standing genetic variation. Specifically, we consider the evolution of a quantitative trait to a gradually changing environment. By means of analytical approximations, we derive the distribution of standing adaptive substitutions and discuss its dependence on the effective population size, the strength of selection and ecological factors.

In line with Barrett and Schluter (2008), we find that compared to new mutations, adaptation from standing genetic variation proceeds, on average, by smaller "steps". Our analysis shows that the genetic basis of adaptation from standing genetic variation crucially depends on the efficacy of selection as defined by the population size, the strength of (stabilizing) selection and the tempo of environmental change. In contrast to studies that consider adaptation from new mutations only (Perron et al. 2008; Bell and Gonzalez

2011; Lindsey et al. 2013; Bell 2013), we find that faster environmental change can enable the population to remain better adapted and to traverse larger distances in phenotype space, when standing genetic variation is the sole source for adaptation.

Synopsis and outlook.

> "When a species is well adapted to the conditions which environ it, it flourishes; when imperfectly adapted it decays; when ill-adapted it becomes extinct."
>
> — Alfred Russel Wallace, *Contributions to the theory of natural selection*

In less than a wink of evolutionary time, we have come from Charles Darwin and Alfred Russel Wallace laying the foundations for evolutionary biology with their description of the "struggle for existence" and the causes of natural selection to the era of transcriptomics, proteomics and whole-genome sequencing that allow evolutionary change to be observed in real time in present-day populations (Hendry and Kinnison 1999; Collins et al. 2007; Lindsey et al. 2013). These technical advances have led to an ever-growing body of data on the genetic basis of adaptation and have widened the gap between data and theory. The aim of this thesis is to advance our theoretical understanding of the adaptive process and to construct a theory which, by explicitly considering genetic and ecological factors, accounts for the inherently dynamic nature of selection and includes standing genetic variation.

All chapters of this thesis stress the importance of the dynamics of the selective environment for adaptation and emphasize that the genetic basis of the adaptive process critically depends on the tempo and mode of environmental change. In particular, in the environmentally-limited regime – where the environment changes slowly and long-term population persistence is most likely (which is consistent with current empirical data; Perron et al. 2008; Bell and Gonzalez 2011; Lindsey et al. 2013) – ecological factors are more important than genetic factors. In contrast, our analysis of the moving-optimum model shows that the genetic basis of adaptation from standing genetic variation has, indeed, very different properties compared to that of *de-novo* mutations. In particular, adaptation proceeds in many small steps and just a few large ones and the prospects of population persistence increase as the environment changes faster, when standing genetic variation is the sole source for evolution. However, quantifying the prospects of population persistence by measuring "maximal sustainable rates of evolution" in natural populations is difficult at best, since stochastic fluctuations due to genetic drift, and

sampling effects can already result in unsustainably high "rates of evolution" – even under constant environmental conditions.

We have also identified some developing areas that significantly increase the realism of the basic models, such as the ones presented in this thesis. Natural populations live in fragmented environments and they can react to environmental change by migration (Pease et al. 1989; Kirkpatrick and Barton 1997; Polechová et al. 2009; Schloss et al. 2012; Duputié et al. 2012; Boeye et al. 2013) and phenotypic plasticity (Chevin et al. 2010b; Reed et al. 2010; Chevin et al. 2012; Gienapp et al. 2013) in addition to genetic evolution.

In fact, the importance of phenotypic plasticity for adaptation to environmental change is well documented (Ghalambor et al. 2007; Hendry et al. 2008; Pfennig et al. 2010; Merilä 2012) and theory suggests that plasticity can facilitate the approach towards a new phenotypic optimum (Lande 2009) and, hence, reduce the risk of population extinction (Chevin and Lande 2010). Its effect, however, strongly depends on cue reliability (Reed et al. 2010) and costs of maintenance (Chevin et al. 2010a), when the population is perfectly adapted. Studies connecting explicit genetics with phenotypic plasticity, though, are sparse (but see Draghi and Whitlock 2012) and there are currently no multivariate plasticity models available in the context of environmental change. Here our models could serve as a starting point for studying the interactions between phenotypic plasticity and genetic evolution.

The effect of migration – similar to that of phenotypic plasticity – is strongly context dependent. While gene flow from maladapted populations can potentially constrain adaptation, it may also promote population persistence by enabling the exploitation of larger geographic ranges and by spreading favourable alleles (Schiffers et al. 2013). A couple of studies also considered a shifting environmental gradient, that is a phenotypic optimum that changes in both space and time (Pease et al. 1989; Kirkpatrick and Barton 1997; Polechová et al. 2009; Duputié et al. 2012). These investigations, however, focused on population persistence rather than on the type, effect-size and origin of mutations contributing to local adaptation. Furthermore, no studies to date have considered the joint effects of plasticity and genetic adaptation in spatially explicit models under environmental change.

Finally, real populations do not evolve in isolation but are embedded in a network of ecological interactions, and so predictions of responses to climate change should be made in a community context. Studies have shown that interspecific competition can have both positive and negative effects on adaptation. While the presence of competitors can

reduce the population size of a focal species and "block" their access to new ecological niches (Johansson 2007; Jones 2008; Jones and Gomulkiewicz 2012; Osmond and Mazancourt 2013; Uecker and Hermisson 2014), competition may facilitate adaptation if a competitor (or predator) "pushes" a focal species towards the direction of the new optimum (Jones 2008; Osmond and Mazancourt 2013; Uecker and Hermisson 2014). The effects of species interactions on the genetic basis of adaptation, however, have not been explored yet.

Together with studying experimental evolution under gradually changing conditions (Collins 2004; Perron et al. 2008; Lindsey et al. 2013) integration of these developing areas promises to significantly increase the realism of the basic models and advance our understanding of species adaptations in their continued "struggle for existence" (Darwin 1859).

Rapid evolution of quantitative traits: theoretical perspectives

M. KOPP, S. MATUSZEWSKI

ABSTRACT. *An increasing number of studies demonstrate phenotypic and genetic changes in natural populations that are subject to climate change, and there is hope that some of these changes will contribute to avoiding species extinctions ("evolutionary rescue"). Here, we review theoretical models of rapid evolution in quantitative traits that can shed light on the potential for adaptation to a changing climate. Our focus is on quantitative-genetic models with selection for a moving phenotypic optimum. We point out that there is no one-to-one relationship between the rate of adaptation and population survival, because the former depends on relative fitness and the latter on absolute fitness. Nevertheless, previous estimates that sustainable rates of genetically-based change usually do not exceed* 0.1 haldanes *(i.e., phenotypic standard deviations per generation) are probably correct. Survival can be greatly facilitated by phenotypic plasticity, and heritable variation in plasticity can further speed up genetic evolution. Multivariate selection and genetic correlations are frequently assumed to constrain adaptation, but this is not necessarily the case and depends on the geometric relationship between the fitness landscape and the structure of genetic variation. Similar conclusions hold for adaptation to shifting spatial gradients. Recent models of adaptation in multispecies communities indicate that the potential for rapid evolution is strongly influenced by interspecific competition.*

1. Introduction

Over the past two decades, it has become clear that evolutionary change can be fast enough to be observed in present-day populations (Hendry and Kinnison 1999; Kinnison and Hendry 2001; Hendry et al. 2008; Gingerich 2009), and that it can directly affect the dynamics of populations and communities (Hairston et al. 2005; Saccheri and Hanski 2006; Kinnison and Hairston 2007; Pelletier et al. 2009). Much recent interest has focused on the possibility that so-called rapid or contemporary evolution leads to "evolutionary rescue", whereby threatened populations avoid extinction by adapting to an altered environment (Barrett and Hendry 2012; Gonzalez et al. 2013). This issue is particularly pressing in the context of global climate change, which subjects large numbers

of populations to shifts in temperature, aridity, seasonal patterns etc. While phenotypic responses to climate change have been documented (Parmesan 2006; Bradshaw and Holzapfel 2006; Hoffmann and Sgro 2011 and this issue), the potential for evolutionary rescue is still unclear (Bell 2013). At the same time, it is often difficult to distinguish changes based on genetic evolution from those due to phenotypic plasticity (Merilä 2012; Merilä and Hendry 2014).

At the basis of many questions in the context of adaptation to environmental change are rates of phenotypic evolution (Hendry and Kinnison 1999; Kinnison and Hendry 2001; Gingerich 2009). These rates are often measured in *haldanes*. One *haldane* is equivalent to a change of one phenotypic standard deviation per generation (for other measures, see discussion in Hendry and Kinnison 1999, and for alternative standardizations and issues of scale, Hereford et al. 2004; Hansen and Houle 2008). Several recent meta-analysis of contemporary evolution yield the following picture: Evolutionary rates above 0.1 *haldanes* are not uncommon (Hendry and Kinnison 1999; Gingerich 2009), even though the majority of rates are lower (Kinnison and Hendry 2001). Rates are higher in populations that are strongly influenced by human activities (Hendry et al. 2008; Darimont et al. 2009). Rates measured over few generations are higher than those measured over many generations (Gingerich 1983; Kinnison and Hendry 2001; Hendry et al. 2008; Gingerich 2009; Westley 2011). Studies that controlled for environmental effects (e.g., by using common garden experiments) find lower rates than those that do not (Hendry et al. 2008), suggesting a role for phenotypic plasticity (Pigliucci and Murren 2003; Hendry et al. 2008; Westley 2011). Over palaeontological timescales, the best-fitting model of phenotypic evolution is one of stasis interrupted by bursts of change (Estes and Arnold 2007; Uyeda et al. 2011).

The aim of this paper is to review quantitative-genetic models that shed light on the potential for rapid adaptation. Our focus will be on the evolution of quantitative traits, that is, traits with continuous variation that are determined by a large number of loci with appreciable standing genetic variation. While we will frequently mention the link between adaptation and population survival, we do not aim for a comprehensive review of evolutionary rescue theory (see Gonzalez et al. 2013 and 14 other articles in a recent theme issue of the *Philosophical Transactions of the Royal Society B*, vol. 368:1610). In particular, we will not treat evolutionary rescue via the fixation of single large mutations (Gomulkiewicz and Holt 1995; Holt and Gomulkiewicz 1997; Orr and Unckless 2008; Uecker and Hermisson 2011; Martin et al. 2013; Kirkpatrick and Peischl 2013).

The structure of the paper is as follows. We first give a detailed description of the basic models of adaptation of single and multiple quantitative traits under various scenarios

of environmental change, including a discussion of "maximal sustainable rates of evolution" (Bürger and Lynch 1995). Subsequently, we discuss four avenues into which the basic models have been extended by recent work: (i) the role of phenotypic plasticity and its interactions with genetic evolution, (ii) determinants of adaptive potential and evolvability, (iii) adaptation to shifting spatial gradients, and (iv) evolution and adaptation in a community context.

2. Basic models

2.1. Modeling approaches

Environmental change. Most theoretical approaches to adaptation in a changing environment are based on models of stabilizing selection with a moving optimum. That is, at any given time, selection favors a specific trait value (or combination of trait values), but this favored phenotype changes over time. The most important scenarios are the following:

- A single, sudden change of the optimum: this is a classic scenario studied in population genetics, and also in recent models about the genetic basis of adaptation (Orr 2005) and evolutionary rescue (Orr and Unckless 2008). It is well suited to study adaptation in invasive species, as well as in species suffering a sudden degradation of their environment.
- Gradual (typically linear) movement of the optimum: This scenario seems best suited to investigate the effects of continued climate change (Fig. 1).
- Random fluctuations of the optimum, either around a constant value or around a linear trend: these fluctuations may or may not show auto-correlation. Such models are useful to study the effects of environmental stochasticity that overlay all climate-driven trends.

Genetic adaptation. The majority of models reviewed here are based on quantitative genetics theory. Evolving traits are assumed to have a polygenic basis and follow a normal distribution with phenotypic variance σ_p^2. In the simplest case (additive genetics, no phenotypic plasticity), σ_p^2 can be decomposed into $\sigma_p^2 = \sigma_g^2 + \sigma_e^2$, where σ_g^2 is the additive genetic variance, σ_e^2 is the environmental variance (variation due to developmental instability and micro-environmental fluctuations), and $h^2 = \sigma_g^2/\sigma_p^2$ is the (narrow-sense) heritability. If phenotypes are measured in units of the environmental variance, σ_e^2 can be

set to 1 (e.g., Bürger and Lynch 1995). The key theoretical tool for studying phenotypic evolution is the Lande equation (Lande 1976a), whose univariate version reads

$$\Delta\bar{z}_t = \sigma_g^2 \beta_t, \tag{2.1}$$

where $\Delta\bar{z}_t$ is the change in mean phenotype after one generation of selection, and $\beta_t = d(\ln \bar{w}_t)/d\bar{z}_t$ is the selection gradient at time t, that is, the derivative of log mean fitness $\bar{w}_t$ with respect to the mean phenotype. Note that equation (2.1) is analogous to the univariate breeder's equation $\Delta\bar{z}_t = h^2 S_t$, where $S_t = \sigma_p^2 \beta_t = \mathrm{cov}(w_t, z_t)$ is the selection differential. A rate of change in *haldanes* can be obtained by standardizing with σ_p, yielding

$$\frac{\Delta\bar{z}_t}{\sigma_p} = h^2 \beta_{\sigma,t}, \tag{2.2}$$

where $\beta_{\sigma,t} = \mathrm{cov}(w_t, z_t)/\sigma_p$ is the variance-standardized selection gradient (Lande and Arnold 1983; Hereford et al. 2004).

For multiple traits, the structure of phenotypic variation is summarized by the matrix **P**, whose diagonal entries contain the phenotypic variances of the individual traits, and whose off-diagonal entries contain the phenotypic covariances. In the standard model, $\mathbf{P} = \mathbf{G} + \mathbf{E}$, where **G** is the (additive) genetic covariance matrix and **E** the matrix of environmental variances and covariances. The multivariate version of Lande's equation is

$$\Delta\bar{\mathbf{z}}_t = \mathbf{G}\boldsymbol{\beta}_t, \tag{2.3}$$

where, for n traits, $\bar{\mathbf{z}}_t = (\bar{z}_{1,t}, \ldots, \bar{z}_{n,t})'$ is the vector of mean trait values (with $'$ denoting transposition) and $\boldsymbol{\beta}_t = (\partial\bar{w}_t/\partial\bar{z}_{1,t}, \ldots, \partial\bar{w}_t/\partial\bar{z}_{n,t})'$ is the multivariate selection gradient, which points in the direction of steepest ascent on the fitness landscape. The response to selection is also influenced by the structure of genetic variation specified in the **G**-matrix. In particular, genetic correlations can cause the response to selection to show a bias towards trait combinations with high genetic variation (see Fig. 2 below; for an introduction to the geometric aspects of multivariate selection, see Walsh and Blows 2009).

The structure of multivariate genetic variation is often analyzed in terms of the eigenvectors of the **G**-matrix (as in a principal component analysis). The eigenvectors (principal components) can be viewed as composite traits (linear combinations of the original

traits) that are genetically uncorrelated (i.e., their covariances are zero) and whose genetic variances are given by the corresponding eigenvalues. Graphically, if the distribution of breeding values (i.e., the average contribution of an individual to the phenotype of its offspring) is multivariate Gaussian, isoclines of this distribution can be represented by ellipses (or higher-dimensional ellipsoids), with axes given by the eigenvectors and their lengths proportional to the roots of the eigenvalues (Fig. 2). The major axis of such an ellipse (i.e., the leading eigenvector of the **G**-matrix) represents the trait combination with a maximum of genetic variation. Is has been called $\mathbf{g}_{\max}$ or the *genetic line of least resistance* (Schluter 1996). Eigenvectors with small (or zero) eigenvalues represent trait combinations with little (or no) genetic variation, into which evolution is severely constrained (Hansen and Houle 2008; Gomulkiewicz and Houle 2009; Kirkpatrick 2009; Walsh and Blows 2009; Chevin 2013). More generally, it is also possible to calculate the amount of variation along any direction of the phenotypic space (Hansen and Houle 2008; Gomulkiewicz and Houle 2009). For the pros and cons of multivariate analysis in quantitative genetics, see Houle et al. (2002), Mezey and Houle (2003), Pigliucci and Kaplan (2006), Blows (2007), Walsh and Blows (2009), Berner (2012) and the commentaries to Blows (2007) in volume 20:1 of the *Journal of Evolutionary Biology*.

Phenotypic plasticity. Phenotypic plasticity in quantitative traits is usually characterized by *reaction norms*, which give the phenotype as a function of an environmental variable. When different genotypes have different reaction norms, plasticity is itself evolvable. While the evolution of plasticity can be modeled in different ways (Via and Lande 1985; De Jong 1995, see also Box 1 in Chevin et al. 2012) most of the models reviewed here focus on linear reaction norms and treat their slope and elevation as quantitative traits (e.g., Lande 2009). The majority of models have studied plasticity in single traits only (but see Gavrilets and Scheiner 1993; Draghi and Whitlock 2012), even though the **G**-matrix is known to be sensitive to environmental conditions (e.g., Tonsor and Scheiner 2007; Husby et al. 2011).

Population dynamics. Models of evolutionary rescue assume that the intrinsic population growth rate depends on the degree of adaptation, that is on mean absolute fitness. Regardless of potential density-dependence, a population will decline if the average number of offspring per individual drops below 1. That is, eventually, population size N is likely to follow

$$N_{t+1} = \bar{w}_t N_t. \tag{2.4}$$

As shown in Appendix 1, the mean fitness $\bar{w}_t$ is generally reduced by two kinds of genetic load (Lande and Shannon 1996; Chevin 2013): a *standing load* due to phenotypic variation and a *lag load* (Maynard Smith 1976) due to deviations of the mean phenotype from the optimum (also called selection load). In many models, survival or extinction of the population depends primarily on the lag load. A crucial point is that population dynamics depend on the mean fitness (eq. 2.4), whereas evolutionary change depends on the fitness gradient (eq. 2.1 or 2.3). Another way of saying this is that population dynamics depends on absolute fitness and evolution on relative fitness (Bell 2013). The relationship between these two quantities is determined by the fitness function: A given fitness gradient can be associated with a higher mean fitness under strong selection than under weak selection (Fig. 1B). This point will be essential in our discussion of sustainable evolutionary rates (see below).

Some predictions from the various models reviewed in this paper are summarized in Table 1.

2.2. Adaptation of a single quantitative trait

Sudden environmental change. In the sudden-change scenario, a population that is well-adapted to its environment is displaced from the fitness peak by a sudden shift of the optimum. Phenotypic evolution is relatively straightforward: The mean phenotype will approach the new optimum exponentially (because the fitness gradient decreases in the vicinity of the optimum) (Lande 1976b). The key question is whether evolution is fast enough in cases where, immediately after the environmental change, the population mean fitness is less than 1. In this case, the population size will initially decline, setting off a "race" between adaptation and extinction. Gomulkiewicz and Holt (1995) showed that evolutionary rescue is possible only if the initial maladaptation after the environmental change is not too large and the initial population size is high.

Gradual environmental change. The situation is quite different if the optimum changes gradually rather than suddenly. In the simplest case, the optimum increases linearly at rate k. This model has been analyzed by Lynch et al. (1991), Lynch and Lande (1993) and Bürger and Lynch (1995) and later been extended by various authors (see below). An excellent summary is given in Bürger and Lynch (1997). Since the behavior of this model is highly instructive, we will describe it in some detail (see also Appendix 1).

Assume again that the original population is well-adapted. As the optimum starts moving, selection becomes gradually stronger (see eq. A4). Consequently, the population

will initially evolve slowly, and the lag between the optimum and the population mean phenotype will increase (the population "slips off" the fitness peak). However, as the distance to the optimum increases, so does the selection gradient, until finally a state of dynamic equilibrium is reached, at which the rate of evolution exactly matches the rate of environmental change (see Fig. 1A and eq. A5). Whether or not the population survives depends on the mean fitness at this distance from the optimum (i.e., on the lag load, which is approximately proportional to k^2; Lande and Shannon 1996). One can thus calculate a *critical rate of environmental change* k_{crit} (eq. A6), which is the maximal rate of change the population can handle. If the environment changes faster than k_{crit} the lag load becomes so large that the population can no longer maintain itself. Extinction usually follows quickly, because the reduction in population size leads to a loss of genetic variation, which further undermines the population's ability to adapt.

Thus, in contrast to the sudden-change scenario, evolutionary rescue in a gradually changing environment requires that the population maintain a positive growth rate at all times. This is a consequence of the "relentless" movement of the optimum, which means that a population that has fallen behind in the race will get no chance to catch up. It also is noteworthy that extinction in this model usually is not due to a lack of genetic variance (except in the final phases of the collapse), nor due the classical "cost of selection" (i.e., the required number of selective deaths, Haldane 1957). Rather, the population dies out because *all* individuals (not just the less adapted ones) have low fitness.

The critical rate of environmental change is directly proportional to the additive genetic variance and the square root of the maximal population growth rate (see eq. A6). The dependence on the width of the fitness landscape – or conversely, the strength of stabilizing selection – is more complex: As shown in the first row of Figure 3, for constant σ_g^2, k_{crit} is maximal at small to intermediate values of the parameter V_s, which measures the effective width of the fitness function. In other words, the population can support the fastest environmental change if stabilizing selection is strong but not too strong. The drop-off in k_{crit} at low or high values of V_s can be explained by the two kinds of genetic load introduced above. On the one hand, very strong selection (i.e., in a steep and narrow fitness landscape; small V_s), induces a high standing load, which reduces the realized growth rate and diminishes the ability of the population to tolerate environmental change. On the other hand, sufficiently weak selection in combination with a moving optimum increases lag load, because the population will follow the optimum at a greater distance. This somewhat counter-intuitive result is due to the fact that, on a flatter fitness landscape, reaching a given selection gradient requires a larger decrease in mean population fitness (see above and Fig. 1). In other words, whereas strong selection keeps the

population close to the optimum at high mean fitness, weak selection, precisely because it is ineffective, allows the population to slip farther off the fitness peak. Therefore, weak selection in combination with a constantly moving optimum represents a "slippery slope" that can be very dangerous for population survival (see discussion in Bürger and Lynch 1995 and Huey and Kingsolver 1993). Bürger and Lynch (1995) also showed that the critical rate of change is further decreased by genetic drift of the mean phenotype in small populations and by stochastic fluctuations of the optimum around the linear trend (see also Björklund et al. 2009).

In many quantitative-genetic models, the additive genetic variance σ_g^2 is assumed to be constant. Over short time-scales, this may be approximately true, but over longer timescales, σ_g^2 is itself subject to evolutionary change, and it is this fact that makes expressions for k_{crit} (such as eq. A6) "deceptively simple" (Bürger and Lynch 1995). Explaining the evolution and maintenance of genetic variation is one of the perennial problems in theoretical population genetics, and no fully satisfactory model has as of yet been found (Barton and Turelli 1989; Bürger 2000; Barton and Keightly 2002; Johnson and Barton 2005; Hill 2010). Before the environmental change, the population may be assumed to be at mutation-selection-drift balance, for which several approximations have been developed (Lande 1976a; Turelli 1984; Bürger 2000; Alvarez-Castro et al. 2009). In the second row of Figure 3, we follow Bürger and Lynch (1995) by showing the predicted values of k_{crit} (in units of the phenotypic standard deviation σ_p, see below) when σ_g^2 is chosen according to the so-called stochastic house-of-cards approximation (Bürger et al. 1989). Doing so takes into account that populations under weak selection have higher genetic variance, which may offset the negative effects of weak selection on the lag load (see above) and lead to a positive relationship between the width of the fitness landscape and k_{crit} (see Huey and Kingsolver 1993). However, this is still not the whole story, because once the optimum starts moving, σ_g^2 is expected to increase. This increase is mainly due to the rise in frequency of previously rare alleles, and it is strongest in large populations (Bürger 1999): For example, under standard values of mutational and selectional parameters, σ_g^2 increases up to 4-fold in populations with $N_e > 5000$. In contrast, selection has little impact on σ_g^2 if $N_e < 200 - 300$ (Bürger 1999), which might explain why genetic variances usually do not increase in artificial selection experiments, as noted by (Johnson and Barton 2005). A useful upper limit for the genetic variance in small populations ($N_e < 500$, Bürger and Lynch 1995) is the neutral expectation $2V_mN_e$, where V_m is the input of genetic variance from new mutations (a typical value is $V_m = 0.001\sigma_e^2$ Lande 1976a; Lynch 1988). In summary, evolution of the genetic variance may increase the prospects of population survival, but mostly in large populations. It should be noted,

though, that the increase in variance takes time and may come too late for populations subject to strong environmental change.

Fluctuating selection. In addition to sudden or gradual changes, most environments are subject to stochastic fluctuations. We have already seen that superimposing fluctuations on a linear trend in the optimal phenotype increases population extinction risk and decreases the critical rate of environmental change k_{crit} (Bürger and Lynch 1995). Here, we briefly discuss the effects of fluctuations around a constant mean. Uncorrelated fluctuations (white noise) in the optimal phenotype resemble a sudden-change scenario that is repeated each generation. Such fluctuations can incur strong selection, but the responses of the population will not add up to large changes over longer timescales (Gingerich 1983; Gibbs and Grant 2006). In addition, genetic responses to selection in one generation are likely to be maladaptive in the next generation, and therefore the lag load will be high (Lande and Shannon 1996; Bürger 1999; Chevin 2013). Consequently, uncorrelated fluctuations do not lead to a significant increase in genetic variance relative to constant stabilizing selection (Bürger 1999). An exception exists, however, if a species possesses dormant stages such as seeds or resting eggs or if generations are overlapping but selection acts only on juveniles. In these cases, the "storage effect" allows the maintenance of genetic polymorphism and, hence, high levels of variation (Chesson and Warner 1981; Hairston et al. 1996). Environmental fluctuations can also select for phenotypic plasticity, provided the state of the environment can be assessed by a reliable cue (Tufto 2000), or for bet-hedging, if there is no such cue (Svardal et al. 2011).

In contrast to uncorrelated fluctuations, autocorrelated fluctuations are more similar to the gradual-change scenario, and a population with sufficient genetic variance can follow the optimum and maintain high fitness (Charlesworth 1993; Lande and Shannon 1996; Chevin 2013). Consequently, autocorrelated fluctuations can lead to significant increases in genetic variation (Bürger 1999).

2.3. Adaptation of multiple correlated traits

When several traits are under selection, the above analyses need to be extended to account for the effects of genetic correlations. As mentioned above, genetic correlations tend to bias the phenotypic response to selection towards the leading eigenvector of the $\mathbf{G}$-matrix, $\mathbf{g}_{\max}$ (the "genetic line of least resistance"; Schluter 1996). In the sudden-change scenario, an evolving population will still reach the new optimum, although not

along the most direct path (Fig. 2A). While the optimum is approached, the lag load decreases as a sum of exponential terms, with rates given by the eigenvalues of the matrix of selection responses (Chevin 2013). Adaptation is fastest and evolutionary rescue is most likely if the angle between the direction of selection and $\mathbf{g}_{\max}$ is small (Schluter 1996; Gomulkiewicz and Holt 1995).

Under gradual environmental change, selection for a moving optimum may cause permanent maladaptation of traits (or trait combinations) that are under pure stabilizing selection (i.e., orthogonal to the direction of the optimum). As illustrated in Figure 2B, the initial response to selection is biased towards $\mathbf{g}_{\max}$, causing the population to rise above the line of the moving optimum, a phenomenon that has been termed the "flying-kite effect" (Jones et al. 2004). Eventually, the rise comes to a halt, as stabilizing selection in the respective direction increases, and the population's trajectory continues in parallel to that of the optimum. Again, population survival will depend on the lag load at this steady state. A critical rate of environmental change can be calculated in analogy to the univariate case (see Appendix 2). It depends not only on the shape of the fitness landscape, but also on the direction of the optimum and the structure of the **G**-matrix. In particular, the critical rate is high if the optimum moves in parallel to $\mathbf{g}_{\max}$, and it is lowest if the optimum moves in a direction of low genetic variation (see Hellmann and Pineda-Krch 2007 for graphical illustrations and a discussion of the consequences for conservation biology).

As in the univariate case, many studies assume that the **G**-matrix is roughly constant over the timescale of interest. Evolution of the **G**-matrix has been studied in a recent series of papers by Jones, Arnold and Bürger (Jones et al. 2003, 2004, 2007, 2012; for review see Arnold et al. 2008). In accordance with previous studies (Barton and Turelli 1987; Bürger and Lynch 1995; Jones et al. 2004), Jones et al. (2012) found that, irrespective of the mode of environmental change (gradual, episodic, stochastic), genetic variance increases in the direction of environmental change. While this facilitates the response to selection, the phenotypic lag also induces a skew in the distribution of breeding values (unfit phenotypes "trailing behind"), which restrains the response to selection. Generally, the two phenomena do not offset each other (Jones et al. 2012), requiring inspection for every individual case. These results highlight the need for caution when iterating the Lande equation or interpreting **G**'s eigenvalues (Kirkpatrick 2009). Under pure stabilizing selection, the **G**-matrix tends to align itself with the fitness landscape, that is, genetic variance is highest in directions with weak selection. **G** depends, however, also on the distribution of new mutations, that is, the **M**-matrix (Jones et al. 2003, 2007), and on gene-flow (Guillaume and Whitlock 2007; Franks et al. 2014).

2.4. Genetic basis of adaptation

The quantitative-genetic models we have considered so far are most accurate if adaptation is based on a large number of loci with small individual effects. In this section, we briefly discuss several issues that arise when this assumption is relaxed.

The first question is how the rate of adaptation is affected by alleles of large effect. If the same total progress towards the optimum can be made by the fixation of either a single allele of large effect or many alleles with small effects, adaptation will be faster in the former case, because selection on the large alleles is more effective (Gomulkiewicz et al. 2010; for the same result in a different context, see also Gavrilets et al. 2007; Rettelbach et al. 2011). In Appendix 3, we calculate the rate of phenotypic evolution due to the fixation of a major allele and show that it can be quite high, at least while the allele is at intermediate frequency. For quantitative traits that are determined by a combination of small- and large-effect loci, Gomulkiewicz et al. (2010) showed that adaptation is fastest when both classes of loci are evolving. For the same situation, Chevin and Hospital (2008) demonstrated that "background"-adaptation from minor loci, by successively reducing the selective advantage of a large-effect allele, can significantly affect its trajectory, and even prevent fixation. The exact outcome crucially depends on the initial allele frequency, the distance from the optimum, and the amount of genetic variation provided by the minor loci.

Another question is, however, how likely beneficial alleles with large effect are in the first place. In a multivariate context, Fisher (1930) used his classical "geometric model" to argue that alleles (i.e., mutations) with large effect that pleiotropically affect multiple traits are most likely to be deleterious. As pointed out by Kimura (1983), however, Fisher neglected the fact that, among beneficial mutations, the few mutations with large effect have a higher fixation probability than the more common mutations with small effects. In the last two decades, numerous theoretical studies have developed predictions for the distribution of phenotypic and fitness effects of both new and fixed mutations (e.g., Martin and Lenormand 2006b, 2008; Keightley and Eyre-Walker 2007; Yeaman and Whitlock 2011), and many models have concluded that the role of mutations with major effects in adaptation is surprisingly large (reviewed by Orr 2005). However, almost all of these models have considered a sudden-change scenario. Under gradual environmental change, results might be very different. In particular, Collins et al. (2007) and Kopp and Hermisson (2007, 2009a,b) showed that a slowly moving optimum favors adaptation by small mutations.

Finally, many authors have studied adaptation and evolutionary rescue from a single large mutation. Since these models usually do not refer to quantitative traits, we only point out the relevant literature: for the probability of evolutionary rescue, see Gomulkiewicz and Holt (1995); Holt and Gomulkiewicz (1997); Orr and Unckless (2008); Uecker and Hermisson (2011); Martin et al. (2013); for the fixation probability of a new mutation in a changing environment, see Uecker and Hermisson (2011); Kirkpatrick and Peischl (2013); Martin et al. (2013); and for the probability of adaptation from standing genetic variation versus new mutations Hermisson and Pennings (2005); Martin et al. (2013).

2.5. Maximal sustainable rates of evolution?

A well-known prediction from the models by Lynch and Lande (1993) and Bürger and Lynch (1995) is that of a "maximal sustainable rate of evolutionary change" on the order of 0.1 *haldanes* or less. This value is simply a ballpark estimate of the critical rate of gradual environmental change, k_{crit} (eq. A6), scaled by the phenotypic standard deviation and parametrized with realistic parameter values (see Appendix 1 and Fig. 3). Since, at the dynamic equilibrium, the population follows the optimum with a constant lag, the rates of environmental and phenotypic change are "formally equivalent" (Bürger and Lynch 1995). For clarity, we will denote the rate of phenotypic change in *haldanes* by $\kappa_{\text{crit}} = k_{\text{crit}}/\sigma_p$ (eq. A7).

Barrett and Hendry (2012) note that it is "tempting" to use $\kappa_{\text{crit}} = 0.1$ as a benchmark for empirically observed evolutionary rates, the idea being that rates near or above this value might be cause for concern since they are not "sustainable" (see also Hendry and Kinnison 1999). Based on earlier meta-analysis (Hendry and Kinnison 1999; Kinnison and Hendry 2001; Hendry et al. 2008), these authors conclude that most rates of change are below 0.1. In contrast, Gingerich (2009) argued that evolutionary rates on the order of 0.1 and 0.3 *haldanes* are common, but his analysis relied on an interpolation technique (log-rate-log-interval plots) that is sensitive to measurement error when real rates of change are small (Hunt 2012 and below). Barrett and Hendry (2012) also warn, however, that theory-derived critical rates rely on "many unrealistic assumptions, such as perpetual persistence under constant environmental change" and that "critical rates for natural populations over time frames of conservation interest could be very different".

There are several points to be made here (see also Appendix 4). First, and obviously, a universal κ_{crit} of 0.1 *haldanes* cannot be more than a rule of thumb. Critical rates may

be higher under strong selection, high heritabilities and in large populations (Fig. 3). Second, some of the reasons for population extinction found by Bürger and Lynch (1995) – such as random but autocorrelated fluctuations in genetic variance – are, indeed, mainly a long-term concern under sustained environmental change. Third, however, the critical rate in equations (A6) and (A7), is simply equivalent to the (instantaneous) rate of evolutionary change that can be achieved without a decrease in population size, as a function of (i) the genetic variance, (ii) the reproductive capacity of the population, and (iii) the shape of the fitness landscape (see discussion of mean fitness vs. fitness gradient above). Faster evolution is possible temporarily, but only at the cost of a reduction in population size. To quantify this effect, in Appendix 4, we estimate maximal rates of environmental and phenotypic change when allowing modest population decline over a limited time frame (e.g., the population is to maintain a minimal size of 50 individuals for 50 generations). As shown in Fig. A1, this provision leads to modest increases in κ_{crit} in large populations (typically around 30%), whereas the effect in small populations is negligible (in particular in light of the stochastic variations discussed below).

In summary, κ_{crit} is, indeed, likely to often be around or below 0.1 *haldanes*. Faster observed rates may be a sign that the population is under stress (e.g., the well-known example of Darwin's finches during a drought, where beak-size increased by 0.66 standard deviations, but 85% of the population died; Grant and Grant 2006) or may indicate that part of phenotypic change is due to plasticity (see below). Temporarily high rates of change may also be achieved by the fixation of a large-effect mutation (Appendix 3).

Small maximal rates of phenotypic change also raise statistical issues (Appendix 5; see also Hendry and Kinnison 1999): Detecting a difference of 0.1 standard deviations between two populations requires very large sample sizes (e.g., almost 800 per population for 50% power in a two-sample t-test with $\alpha = 0.05$). On the other hand, differences of this magnitude can easily be created by sampling effects (Fig. A2, A3; Kinnison and Hendry 2001; Hunt 2012). Indeed, the mean absolute differences in units of phenotypic standard deviations between two samples of size n drawn from the same population is $2/\sqrt{n\pi}$ (Hunt 2012), which equals 0.113 for $n = 100$. In finite populations, similar effects occur due to genetic drift and environmental variance (even if the whole population is sampled). The variance of the mean phenotype due to genetic drift is σ_g^2/N_e, with N_e being the effective population size (Lande 1976a). By a calculation analogous to the one in Hunt (2012), the mean generation-to-generation rate in *haldanes* due to drift is $2\sqrt{h^2/(\pi N_e)}$, which is 0.025 for $N_e = 1000$ and $h^2 = 0.5$. Similarly, the contribution of environmental variance (i.e., genotype-independent random variation in individual phenotypes) to the mean rate of phenotypic change is $2\sqrt{(1-h^2)/(\pi N)}$ (with N

being the census population size). Together, these two sources of variation may dominate the generation-to-generation changes in the mean phenotype of small populations (Appendix 5, Fig. A3, A4). In summary, maximal sustainable rates of evolutionary change might often be of the same order than various sources of stochastic noise, something which should be kept in mind when interpreting evolutionary rates measured over short timescales.

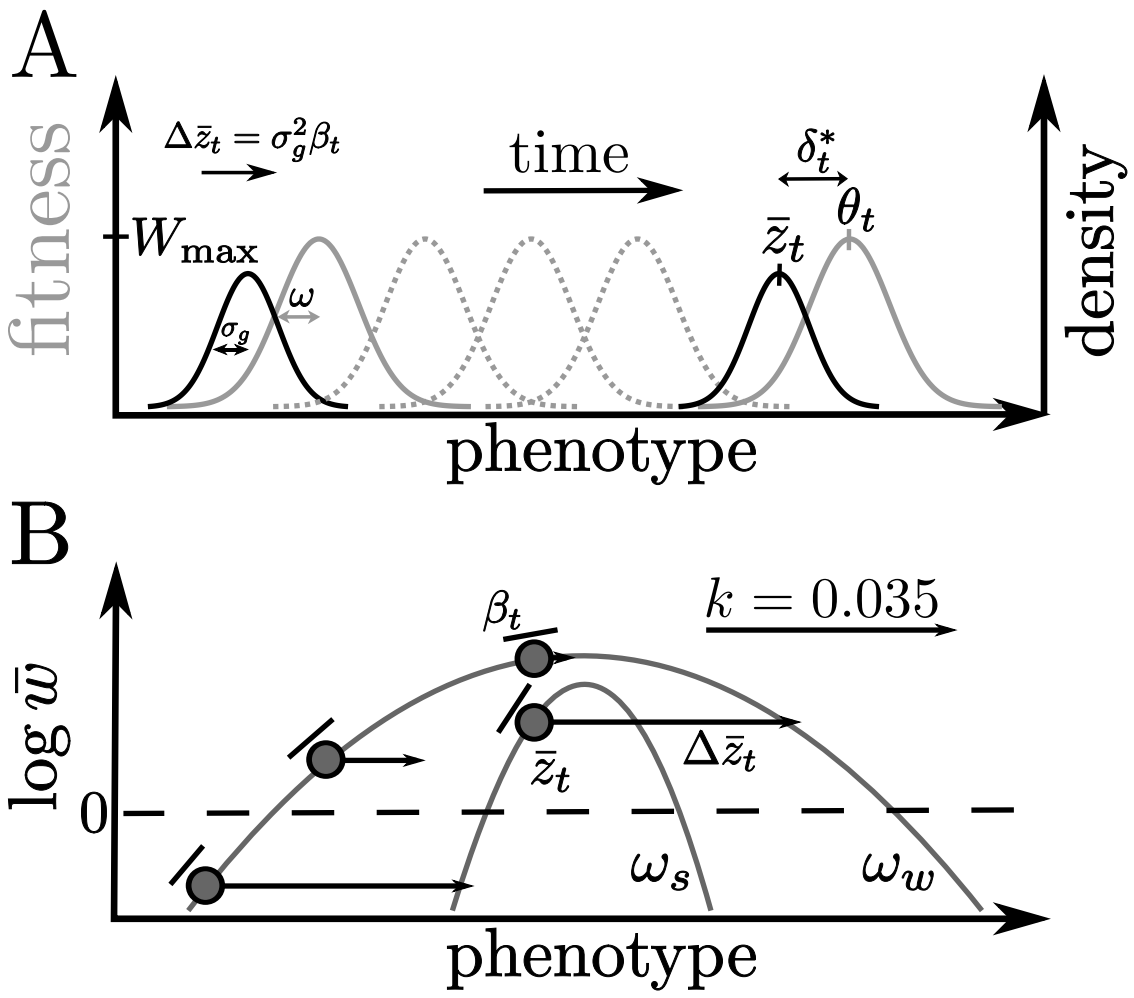

Figure 1 – Illustration of trait evolution in the one-dimensional moving-optimum model. (A) Solid and dotted grey curves represent the fitness landscape at different points in time (eq. A2), whose width is determined by ω. θ_t is the optimal phenotype, which moves at constant speed ($\theta_t = kt$). The black curves represent the distribution of breeding values in the population (mean $\bar{z}_t$, variance σ_g^2). The mean phenotype evolves according to eq. (2.1). At the dynamic equilibrium, it follows the optimum with a constant lag δ_t^*. (B) illustrates the relation between rate of evolution and extinction risk. The grey curves show the log mean fitness as a function of the mean phenotype $\bar{z}_t$ for two different fitness functions with widths ω_s and ω_w, respectively. The rate of evolution, given by the horizontal arrows is determined by the fitness gradient β_t, indicated by the black lines. The vertical position of the population gives its mean (log) fitness. In the Figure, the optimum is assumed to move at rate $k = 0.035$, and the population placed at the narrow fitness curve follows at this pace while maintaining a positive growth rate ($\bar{w} > 1$). With the wide fitness function, however, the same rate of evolution requires a larger distance from the optimum, such that the growth rate is negative and the population goes extinct.

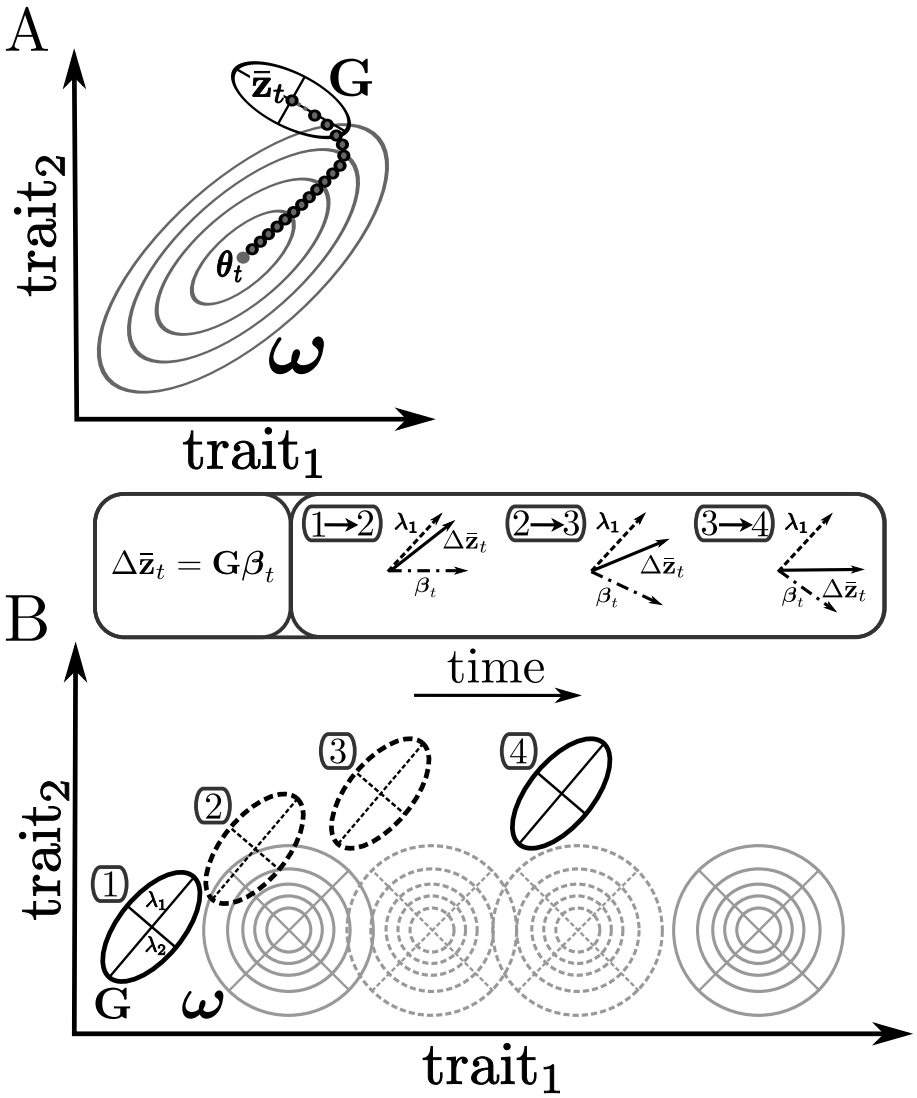

Figure 2 – Illustration of adaptation involving two genetically correlated traits. (A) Adaptation after a sudden environmental change; the new optimum $\boldsymbol{\theta}_t$ is constant. Grey lines illustrate the fitness surface, defined by the matrix $\boldsymbol{\omega}$. The distribution of breeding values defined by the **G**-matrix is illustrated by the black ellipse, whose center is the mean phenotype $\bar{\mathbf{z}}_t$ and whose axis are the eigenvectors of **G**. The initial response to selection is biased towards the leading eigenvector, that is, the genetic line of least resistance (Schluter 1996). (B) Adaptation to a moving optimum. Grey circles show the fitness landscape at four different points in time. Black ellipses show the corresponding positions of the population (represented by the **G**-matrix). The insets at the bottom show the leading eigenvector of **G**, λ_1, the selection gradient $\boldsymbol{\beta}_t$ and the response to selection $\Delta\bar{\boldsymbol{z}}_t$ at time-points 1, 2 and 3, respectively. Because the initial response is biased towards the leading eigenvector, the population "rises" above the line of the moving optimum (i.e., the flying-kite effect; Jones et al. 2004). This rise comes to a halt as the tendency to follow the line of least resistance is balanced by the selection gradient, resulting in horizontal movement of the population.

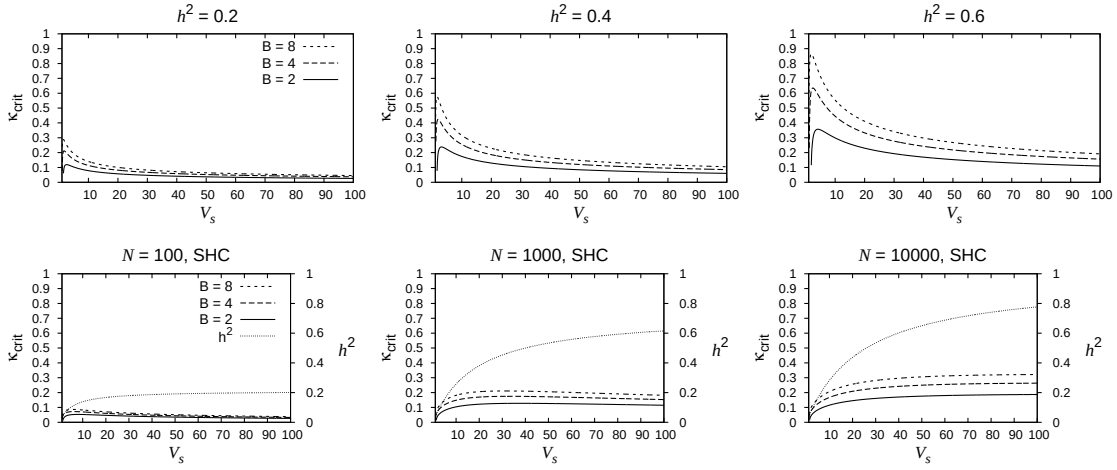

Figure 3 – The critical rate of phenotypic evolution, $\kappa_{\text{crit}} = k_{\text{crit}}/\sigma_p$ (eq. A7) expressed in *haldanes*, for the one-dimensional moving-optimum model (A2) (after Bürger and Lynch 1995), as a function of the width of the fitness function $V_s = \omega^2 + \sigma_e^2$ (with $\sigma_e^2 = 1$), for various values of the reproductive potential B. The top row shows results for three different values of heritability $h^2 = \sigma_g^2/(\sigma_g^2 + \sigma_e^2)$. In the bottom row, σ_g^2 has been set to the value predicted by the stochastic house-of-cards (SHC) approximation under pure stabilizing selection for three values of the population size N. The SHC approximation is given by $\sigma_g^2 = 2V_m N_e/(1 + \alpha^2 N_e/V_s)$ (Bürger and Lynch 1995), where V_m is the mutational variance, α^2 is the variance of the effect of new mutations, and $N_e \approx 2BN/(2B - 1)$ (Bürger and Lynch 1995) is the effective population size. The figures are for $V_m = 0.001$ and $\alpha^2 = 0.05$. The thin dotted line gives the heritability h^2 associated with σ_g^2(SHC).

3. The role of phenotypic plasticity

So far, we have only considered genetic adaptation. However, many observed responses to climate change are likely to be plastic (Gienapp et al. 2008; Hendry et al. 2008; Merilä 2012), and assessing the relative importance of plastic and genetic changes is precisely the aim of this special issue of *Evolutionary Applications*. Yet, in its basic form, the question is empirical and cannot be answered by theory alone. While quantitative genetic models can make some tentative predictions about the maximal rates of genetically based evolution (see above), it seems impossible to make general statements about the range and scope of plasticity. Here, we will instead focus on reviewing models that investigate the interaction between plasticity, population dynamics and genetic evolution. Because several important aspects have already been reviewed elsewhere (Ghalambor et al. 2007; Chevin et al. 2012), our treatment can be short.

Ecological models have investigated the effect of plasticity on population stability and extinction risk in the absence of evolution. Community models including so-called trait-mediated indirect effects (Werner and Peacor 2003) frequently find that phenotypic plasticity mediated by species interactions (e.g., inducible defenses against predators; Tollrian and Harvell 1999) can stabilize population dynamics, even though such a stabilizing influence is not universal (Kopp and Gabriel 2006). If plasticity increases the range of conditions under which a community is stable, it reduces the risk of species extinctions after an arbitrary environmental change ("plastic rescue"; Kovach-Orr and Fussmann 2013).

For a single population, Reed et al. (2010) studied the impact of phenotypic plasticity on population extinction risk in a randomly fluctuating environment. They found that adaptive plasticity decreases extinction risk, unless the magnitude of plastic responses exceeds an optimal level set by cue reliability (strong responses to unreliable cues tend to be harmful). Chevin et al. (2010) included phenotypic plasticity into the moving-optimum model of Lynch and Lande (1993) and Bürger and Lynch (1995). Assuming a linear reaction norm with slope less than one, plasticity essentially reduces the speed of environmental change perceived by the population. Plasticity thus increases the critical rate of environmental change k_{crit} that separates population survival from extinction. In consequence, it increases the maximal rate of phenotypic change, while simultaneously decreasing the rate of genetic evolution. This effect may be reversed at high levels of plasticity if plasticity itself is costly (and hence, reduces the mean fitness of the population).

Gienapp et al. (2013) recently applied both the Chevin et al. (2010) and the Bürger and Lynch (1995) model to anticipate evolution of egg-laying dates in great tits from a well-studied Dutch population. Egg-laying date in this species is a phenotypically plastic trait that depends on spring temperature and is selected to coincide with the peak in caterpillar abundance. Using various modeling techniques, the authors show that, despite plasticity, global warming will create a mismatch between the optimal and realized egg-laying dates, which might threaten population persistence unless it can be closed by genetic evolution. By focusing on the predicted mismatch, the authors were able to parametrize the Bürger and Lynch (1995)-model (i.e., eq. A6), even though this model was not built to deal with plasticity. They conclude that, even under a mild climate-change scenario, the predicted rate of environmental change (from the point of view of the population) is close to the theoretical maximal sustainable rate. To parametrize the Chevin et al. (2010)-model, (Gienapp et al. 2013) assumed that both optimal and realized egg-laying dates correlate with mean spring temperature (measured between mid-March and mid-April). Although the Chevin et al. (2010)-model seems to be more suitable for the analysis of a plastic trait, its results are less plausible than those obtained from the Bürger and Lynch (1995)-model. In particular, the model predicts that population survival will be facilitated by fast environmental change. The authors argue that this counterintuitive prediction is an artefact, which arises because, with faster temperature increase, mean spring temperature becomes less and less correlated with the true causal variable determining optimal egg-laying date. This highlights the general problem that, frequently, the variables we can measure are just proxys for one or more causal factors. If the proxy is bad, any model will perform poorly. Despite these issues, the study by Gienapp et al. (2013) is exemplary in its combined use of long-term empirical data, climate-change predictions, and models for future optimal and realized behavior.

In the following we briefly review models in which plasticity can itself evolve. Conditions for the evolution of plasticity are fairly well understood. Plasticity is adaptive if individuals encounter different environmental conditions that favor different phenotypes and that can be assessed by a reliable cue (e.g., Tollrian and Harvell 1999; Ghalambor et al. 2007). Its evolution may be limited by functional constraints, unreliable cues (Tufto 2000), and costs for the necessary sensory and developmental machinery (DeWitt et al. 1998; van Buskirk and Steiner 2009). More recently, however, phenotypic plasticity has been advocated as not only a product, but also a driver of genetic evolution (West-Eberhard 2003; for recent reviews, see Ghalambor et al. 2007; Pfennig et al. 2010; Wund 2012; Wennersten and Forsman 2012). The basic idea is that new phenotypes first

appear as a result of environmental induction and only later are fixed via "genetic assimilation" or "genetic accommodation". Here, genetic assimilation corresponds to a loss of plasticity, such that expression of the phenotype becomes independent of environment cues. Genetic accommodation is a more general "fine-tuning" of the novel phenotype via changes in allele frequencies, potentially facilitated by a release of hidden genetic variation (Hermisson and Wagner 2004; Moczek 2007; for more conceptual discussion, see West-Eberhard 2005; Crispo 2007; Ghalambor et al. 2007). The more ambitious versions of this hypothesis – that environmental induction can be at the basis of "evolutionary novelties" (West-Eberhard 2003; Pigliucci et al. 2006; Uller and Helanterä 2011) – appears unaccessible to classical population-genetics modeling. Here, we focus on the less far-reaching question of the role of plasticity in the evolution of existing quantitative traits.

Phenotypic plasticity has traditionally been viewed as delaying genetic evolution. This is certainly true if plasticity is sufficient to ensure continued high fitness of a population in a changing environment. However, there are other scenarios in which plasticity may, indeed, speed up or facilitate genetic change. A simple case is the Baldwin effect (Baldwin 1896; Crispo 2007), where plasticity (specifically, learning) allows a population to survive in a new or changed environment, thereby enabling future genetic adaptation (for models, see Ancel 1999; Pál and Miklós 1999; Ancel 2000; Paenke et al. 2007). Furthermore, plasticity can influence the course of evolution by bringing a population into the domain of attraction of a specific adaptive peak. The probability of a peak shift is highest if plasticity is of intermediate strength (Price et al. 2003). Both mechanisms may play a role in biological invasions as well as adaptation to climate change.

Recently, Lande (2009) proposed a simple model for the role of plasticity in adaptation to an abrupt environmental shift. He considered the evolution of a quantitative trait that is determined by linear reaction norms. That is, for each individual, the trait value is a linear function of an environmental variable, with genetic variation in the slope and intercept of this function (see also Gavrilets and Scheiner 1993). Under the original conditions, a modest level of plasticity (i.e., an intermediate slope of the reaction norm) is favored in a slightly fluctuating environment with constant mean and imperfect cues. At this stage, reaction-norm slope varies between individuals, but the mean phenotype is relatively homogeneous (canalization). When the mean environment changes, genetic variance is increased due to differential plastic responses (decanalization), and selection favors individuals with steep reaction norms, which can best adjust to the new conditions. That is, the population evolves towards the new optimum via the evolution of increased plasticity, allowing high rates of phenotypic change. Subsequently, the reaction norm intercepts

increase and slopes decrease, again reaching the optimal degree of plasticity in the new environment (genetic assimilation). Chevin and Lande (2010) added population dynamics to this model and showed that evolving plasticity strongly increases the probability of evolutionary rescue after a sudden environmental change.

4. What determines adaptive potential?

Ideally, we would like to be able to predict which species have the potential to adapt to rapid climate change (Williams et al. 2008; Huey et al. 2012). Obviously, phenotypic plasticity will help (see above), but theory can say little more than that. With regard to genetic adaptation, the adaptive potential depends most directly on the genetic variation that is available in the direction of selection. In addition, we may also ask what kind of genetic architectures and evolutionary histories facilitate rapid adaptation. We will discuss these two issues in turn.

4.1. Genetic variance and genetic constraints

For single traits, a short-term measure of adaptive potential is given by the additive genetic variance (see eq. 2.1), and a lack of such variance corresponds to a genetic constraint (i.e., adaptive potential and genetic constraints are two sides of the same coin). An absolute constraint is present if genetic variance is zero, and a relative constraint if it is low. Gomulkiewicz and Houle (2009) pointed out that, if adaptation is too slow to avoid extinction, a relative (or quantitative) constraint is effectively transformed into an absolute constraint. They coined the term "demographic constraint" to refer to this situation and calculated "critical amounts of genetic variance" and "critical heritabilities" that are necessary to prevent extinction under scenarios of sudden and gradual environmental change.

In the multivariate case, an additional source of genetic constraints may arise from genetic correlations. Indeed, even if every single trait has positive genetic variance, the variance for certain trait combinations may be zero (Dickerson 1955). In this case, the **G**-matrix is singular (Lande 1979), that is, at least one of its eigenvectors has a zero eigenvalue. If the selection gradient is parallel to such an eigenvector, it will produce no effect. Regardless of the direction of selection, evolution will be possible only in a lower-dimensional subspace of the original phenotype space (e.g., along a line in two dimensions or a plane in three dimensions). A singular **G**-matrix might be an extreme case (and is difficult to infer statistically). However, relative constraints arise in the same way, whenever an eigenvalue is positive but small. Using their concept of demographic

constraints, Gomulkiewicz and Houle (2009) calculated critical values for the smallest eigenvalue of **G** in the worst-case scenario that selection acts exactly in the direction of the corresponding eigenvector.

What is the overall role of genetic correlations in constraining the rate of adaptation? – Walsh and Blows (2009) argued that strong multivariate constraints (weak variation in the direction of selection) might, indeed, be common and could explain the frequent observation of slow evolutionary change despite strong selection on (individually) variable traits. To quantify the distribution of genetic variation, Kirkpatrick (2009) defined a measure of "effective dimensionality"

$$n_d = \sum_{i=1}^{n} \frac{\lambda_i}{\lambda_1}, \tag{2.5}$$

where the λ_i denote the eigenvalues of the **G**-matrix ordered from the largest (λ_1) to the smallest (λ_n). If genetic variation is uniformly distributed among the eigenvectors, n_d takes it maximal value of n, whereas it is minimal (equal to 1) when genetic variation is only present along a single axes. A review of empirical estimates of n_d suggests that it is often (much) smaller than the number of traits considered (Kirkpatrick 2009). Thus, genetic variation seems to be concentrated around a few dimensions, meaning that the ability of populations to respond to arbitrary selection pressures may be severely reduced.

However, an alternative approach by Agrawal and Stinchcombe (2009) yields more nuanced results. These authors proposed to compare the increase in mean fitness in response to a given selection gradient for the full **G**-matrix with the expected response when assuming a (hypothetical) modified **G**-matrix in which all off-diagonal entries (i.e., all covariances) have been set to zero. Using data from empirical estimates of **G**- (or **P**)-matrices and selection gradients, they found that removing genetic correlations sometimes increases and sometimes decreases the rate of adaptation, and that often, the effect is minor. In this context, it is worth pointing out that genetic correlations do not necessarily decrease the variance in a particular direction. For example, adding arbitrary covariances to a diagonal **G**-matrix can only increase genetic variation in the direction of the leading eigenvector (Horn and Johnson 1985, p. 194).

Theoretical studies have used two approaches to quantify genetic constraints (for a review of measures, see Walsh and Blows 2009). If the selection gradient is known, adaptability and constraints should be expressed relative to its direction. A sophisticated

set of measures was proposed by Hansen and Houle (2008), who distinguish "respondability" (the magnitude of overall phenotypic change in response to selection in a given direction with unit magnitude), "evolvability" (the magnitude of response in the direction of selection), "conditional evolvability" (the magnitude of response in a selected traits if correlated traits are forced to remain constant), and "autonomy" (the fraction of genetic variation in a trait that is independent of potentially constraining characters). For cases where the direction of selection is not known, several authors have calculated mean rates of adaptation over a distribution of possible selection gradients (Hansen and Houle 2008; Kirkpatrick 2009; Chevin 2013). When the distribution of selection gradients is uniform, genetic correlations have no effect on the mean rate of adaptation, because high rates in directions of large variation are offset by low rates in directions of small variation (Hansen and Houle 2008; Kirkpatrick 2009). When the distribution of gradients is not uniform, however, the mean rate of adaptation is highest if selection gradients tend to coincide with directions of large genetic variation (Chevin 2013).

4.2. Other determinants of adaptive potential

We now go on to discuss a broader view of adaptive potential and evolvability. Sexual reproduction and genetic recombination have long been hypothesized to facilitate adaptation to changing environments (e.g., by bringing together alleles on the same genome and reducing the effect of clonal interference). For a gradual-change model, this was confirmed via simulation by Bürger (1999) (see also Charlesworth 1993; Waxman and Peck 1999). In particular, the increase in genetic variance under directional selection (see above) is almost absent in asexual populations.

Several theoretical studies have compared adaptation in (sexual) haploid and diploid populations, but the results are complex. Haploid populations can be expected to evolve faster than diploid populations, because selection is more efficient in haploids (Orr and Otto 1994; Otto and Gerstein 2008), and this was confirmed experimentally in yeast (Gerstein et al. 2011). Nevertheless, haploid populations were invaded by diploid strains (Gerstein and Otto 2011). While in this case the "cryptic fitness advantage" was attributed to negative frequency-dependent selection, a more general advantage to diploidy was proposed by Sellis et al. (2011). Using the framework of Fisher's geometric model, these authors argued that heterozygote advantage is a natural consequence of adaptation in diploids, at least in populations that are close to a phenotypic optimum. (The reason is that mutations often have smaller phenotypic effects in heterozygotes than in homozygotes, such that heterozygotes may have a fitness advantage, while homozygotes already overshoot the optimum – a probability that increases with the number of phenotypic

dimensions.) Since heterozygote advantage favors the maintenance of polymorphism, diploids are expected to have higher levels of genetic variation, conferring them an increased adaptive potential in case of rapid environmental change. Indeed, simulations showed that, in fluctuating environments, diploid populations maintained higher mean fitness than haploids, despite a larger standing load (Sellis et al. 2011).

Again using Fisher's geometric model, Orr (2000) argued that evolvability is reduced in complex organisms, because mutations are more likely to have negative pleiotropic side effects. This "cost of complexity" can, however, be reduced by a modular organisation (Welch and Waxman 2003). Indeed, several studies have concluded that "effective complexity" is low in many organisms (e.g., Martin and Lenormand 2006a; Lourenco et al. 2011). Such low dimensionality/pleiotropy is predicted to increase the proportion of beneficial mutations with large effect, which in turn can facilitate adaptation (Gomulkiewicz et al. 2010). Gene-network models also predict that small network size leads to an increased rate of adaptation, faster population recovery and higher critical rates of environmental change (Malcom 2011a,b). Along similar lines, mutational robustness (i.e., the probability for genotypes connected by mutations to express the same phenotype) can paradoxically increase the adaptive potential of a population by allowing synonymous genetic variants to accumulate, thus increasing the mutational neighborhood of a given phenotype (Gavrilets 1997; Fontana and Schuster 1998; Wagner 2008; Draghi et al. 2010).

Finally, adaptive potential is likely to be influenced by a species' evolutionary history. In particular, species that have evolved in variable environments are more likely to survive future environmental change than species that have long lived under very constant conditions. The idea is not only that past fluctuations endow a species with increased genetic variation (see above), which has been pre-tested by selection in past environments (Masel 2006; Wagner 2007; Hayden et al. 2011), different habitats, or even in another species (e.g., introgression) (Rieseberg et al. 2003; Barrett and Schluter 2008), but also that the species may have evolved increased plasticity and a more flexible genetic architecture (Hansen 2006). Indeed, the last two points might be related. Several recent models have shown that genetic networks that evolved to express plasticity also allow for faster genetic adaptation (Fierst 2011; Espinosa-Soto et al. 2011; Draghi and Whitlock 2012).

On the other hand, species that have evolved under highly stable conditions are expected to be the most sensitive to environmental change (Overgaard et al. 2011). In particular,

there is concern that tropical ectoterms might be unable to resist increasing temperatures (Janzen 1967; Ghalambor et al. 2006; Deutsch et al. 2008; McCain 2009; Hoffmann et al. 2012; Urban et al. 2014). Indeed, such species are characterized by narrow thermal tolerance curves (Amarasekare and Savage 2012) and have narrow altitudinal ranges (McCain 2009). If genetic variation in the optimal temperature is proportional to the width of the thermal tolerance curve (as has been demonstrated for *Drosophila*; Kellermann et al. 2009; Schilthuizen and Kellermann 2014) they should also have reduced critical rates of environmental change (Huey and Kingsolver 1993). Quantitative predictions about extinction risk are difficult, however, because most studies on thermal tolerances provide only relative, not absolute, fitnesses (Deutsch et al. 2008; Martin and Huey 2008; Bonebrake and Mastrandrea 2010).

5. Adaptation in space

Real populations are distributed in space, and they can react to environmental change by migration in addition to genetic evolution and plasticity (Parmesan 2006; Schloss et al. 2012). Here, we are not primarily interested in range shifts, but instead focus on the effects of gene flow on local adaptation in changing environments.

A natural extension of the gradual-change model discussed above considers a shifting environmental gradient, that is, an optimum that changes in both space and time. Building on earlier models by Pease et al. (1989), Kirkpatrick and Barton (1997) and Polechová et al. (2009), Duputié et al. (2012) recently investigated adaptation of multiple quantitative traits in response to such a shifting gradient. In particular, they addressed how multivariate genetic constraints and gene flow alter the adaptive potential. While gene flow from maladapted populations can potentially constrain local adaptation, it may also promote population persistence by enabling the exploitation of larger geographic ranges and by spreading favorable alleles (Schiffers et al. 2013). Consequently, regardless of the number of traits under selection, the critical rate of environmental change is maximized when dispersal is neither too weak nor too strong (Alleaume-Benharira et al. 2006; Duputié et al. 2012). Population persistence also strongly depends on the slope of the spatial gradient. When the gradient is weak (i.e., the loss of fitness per unit space is small), the population remains well-adapted over a wide range. Conversely, a steep gradient constrains the range. In this case, population persistence depends heavily on the geometric relation of the **G**-matrix, the shape of the fitness landscape, and the direction of the spatial gradient. In particular, adaptive constraints are minimal whenever the spatial gradient is collinear with the direction of weakest stabilizing selection and largest genetic variance. Similar to the "flying-kite effect" (Jones et al. 2004), Duputié

et al. (2012) also found that, when there is indirect selection on negatively correlated traits, adaptation in one trait can cause another trait to develop a spatial gradient in the direction opposite to its optimum. When genetic variances are allowed to evolve (as a consequence of selection and gene flow, see above), univariate models have shown that sufficiently large populations can be perfectly adapted over their whole range, albeit at the cost of an increased standing load (Barton 2001; Polechová et al. 2009; Bridle et al. 2010).

The effect of gene-flow on the **G**-matrix has been studied by Guillaume and Whitlock (2007). Using a continent-island model, these authors showed that a migration rate of about one individual per generation increases the size of **G** by up to 3-fold, and may cause its shape and orientation to "flip" (albeit only over time-scales of several hundred generations). These effects are particularly pronounced if other factors acting on **G**, such as the input of mutational variance and mutational or selective correlations, are weak.

The effect of phenotypic plasticity on local adaptation and the colonization of new habitats has been studied by Chevin and Lande (2011) and Thibert-Plante and Hendry (2011). Both studies found that plasticity can facilitate colonization of new habitats, especially if it is expressed after migration (i.e. juvenile dispersal). However, no studies to date have considered the joint effect of plasticity and genetic adaptation in spatially explicit models under environmental change.

6. Beyond single species

Real populations do not evolve in isolation but are embedded in a network of ecological interactions, and so predictions of responses to climate change should be made in a community context. Several studies have investigated the effects of interspecific competition on the rate of adaptation and the likelihood of evolutionary rescue. Both positive and negative effects are possible. The presence of competitors can reduce the rate of adaptation in a focal species by reducing its population size (and, hence, genetic variance or mutational input) and by "blocking" the access to new ecological niches (Johansson 2007; Jones 2008; Jones and Gomulkiewicz 2012; Osmond and Mazancourt 2013). This effect increases the lag load, decreases the critical rate of environmental change and can contribute to species extinctions. On the other hand, competition may also facilitate adaptation if a competitor (or predator) "pushes" a focal species in the direction of the new optimum (Jones 2008; Osmond and Mazancourt 2013). Osmond and Mazancourt (2013) argue that both effects can be found in recent studies of character displacement

in Darwin's finches (Grant and Grant 2006). Evolution may also be sped up by competitive release if climate change causes a competitor to go extinct (Poloczanka et al. 2008).

In the presence of a shifting spatial gradient (see above), community evolution depends on the interaction of local adaptation and dispersal (de Mazancourt et al. 2008; Urban et al. 2012a,b). De Mazancourt et al. (2008) used simulations of a multi-patch model to show that species often shift their range to new habitats rather than adapting to their altered current habitat, and that this effect is stronger in species-rich communities. Urban et al. (2012a) use the term "competitive constraint" to describe the situation where a local species is prevented from adapting to a changing environment because its habitat is being invaded by a competing species already adapted to the new conditions. This effect is a possible explanation for niche conservatism (Wiens et al. 2010) during contemporary evolution. The opposite effect is also possible, however: local adaptation of a resident species can prevent the establishment of a later-arriving invader (monopolization effect, Urban and de Meester 2009; Urban et al. 2012a. And even mal-adapted residents can slow range expansions of dispersing species into newly available habitats ("boxcar effect": species can climb climate gradients only as fast as species further up the line; Urban et al. 2012b). In summary, predicting community response to environmental change requires considering the interactions of two local processes (local community dynamics; local adaptation) and two regional processes (immigration from regional species pool; immigration from regional genotype pool; Urban et al. 2012a).

If we move beyond pairwise interactions, both rapid evolution and phenotypic plasticity have been shown to contribute to community stability (e.g., Werner and Peacor 2003; Yamamichi et al. 2011). Kovach-Orr and Fussmann (2013) coined the terms "evolutionary and plastic rescue" to describe situations where this enhanced stability prevents species extinctions after an environmental change. Finally, evolutionary responses to climate change in complex communities will not always increase the chances of population survival, but may instead lead to "evolutionary suicide" (Ferrière and Legendre 2013).

7. Conclusions

We have reviewed theoretical models of adaptation to changing environments, with a focus on evolutionary rates of quantitative traits. Unlike models of evolutionary rescue by single mutations, the majority of quantitative-genetic models consider gradual rather than abrupt environmental change. Early models for single traits have introduced the

concept of a critical rate of environmental change or maximal sustainable rate of evolution, beyond which long-term persistence is not possible (Lynch and Lande 1993; Bürger and Lynch 1995). Subsequently, this concept has been extended to include multivariate selection (Gomulkiewicz and Houle 2009), spatial variation (Duputié et al. 2012) and phenotypic plasticity (Chevin et al. 2010). Despite the added complexity, it seems unlikely that genetic evolution can frequently produce rates of change beyond 0.1 *haldanes* for more than a few generations. Higher observed rates are thus likely to be due to phenotypic plasticity, or to be accompanied by population decline. Empirical tests of this theory are challenging (Gomulkiewicz and Shaw 2013), in part due to a strong impact of non-selective stochastic factors on observed evolutionary rates, and only one study (Gienapp et al. 2013) has attempted to estimate the critical rate of change for a natural population (for estimates based on physiological models and laboratory data, see Huey and Kingsolver 1993 and Willi and Hoffman 2008). We hope that, in the future, more such estimates will become available from well-studied populations. Another promising avenue is experimental evolution under gradually changing conditions (Collins 2004; Perron et al. 2008; Lindsey et al. 2013).

We have also identified four developing areas that significantly increase the realism of the basic models. These include the interactions between phenotypic plasticity and genetic evolution, the role of genetic architecture for the adaptive potential, adaptation to shifting spatial gradients, and the influence of interspecific interactions on rates of adaptation. The former two concern mainly internal (organismal) features, whereas the latter two are about external (environmental) factors. Further integrating these various models promises to significantly advance our understanding of species adaptations to climate change.

Acknowledgements

We thank Reinhard Bürger for helpful discussions and Andrew Hendry and three anonymous reviewers for constructive comments on this manuscript. This study was partially supported by FWF-grant P 22581-B17 to MK.

Mode of Env. Change	Phenotypic Evolution	Survival/Extinction	Effects of Plasticity
Sudden Change			
Single Trait	Change in mean phenotype described by univariate Lande equation (eq. 2.1). Exponential approach to new optimum (Gomulkiewicz and Holt 1995).	Maximal amount of environmental change the population can handle depends on width of fitness function, intrinsic growth rate, initial population size, and genetic variation (Gomulkiewicz and Holt 1995)	Approach to new optimum is facilitated by temporary increase in phenotypic plasticity and a concomitant release of hidden genetic variation (Lande 2009). Plasticity reduces extinction risk (Chevin and Lande 2010).
Multiple Traits	Change in mean phenotype described by multivariate Lande equation (eq. 2.3). Trajectory to new optimum biased towards genetic line of least resistance (Schluter 1996). Lag load decreases roughly exponentially (Chevin 2013).	As for single trait. Extinction risk depends on genetic variance in direction of selection (Gomulkiewicz and Houle 2009).	No models available for the context of environmental change.
Gradual Change			
	Population follows the optimum with a constant lag (Lynch and Lande 1993). Trait correlations can induce permanent maladaptation in traits under stabilizing selection ("flying kite effect"; Jones et al. 2004). Genetic variance increases (Bürger and Lynch 1995; Bürger 1999).	Critical rate of environmental change (eq. A6) increases with genetic variance in direction of moving optimum and with intrinsic growth rate; is maximal at intermediate strength of selection (Lynch and Lande 1993; Bürger and Lynch 1995; Gomulkiewicz and Houle 2009), see Fig. 3.	Adaptive plasticity reduces the perceived speed of environmental change ⇒ increases critical rate of change, decreases phenotypic lag and decreases rate of genetic evolution. Effects may be counteracted by costs of plasticity (Chevin et al. 2010).
Random Change			
	Population's ability to track the optimum increases with autocorrelation of fluctuations (Lande and Shannon 1996; Chevin 2013). Autocorrelated fluctuations increase genetic variance, whereas uncorrelated fluctuations do not (Bürger 1999).	Extinction risk elevated if fluctuations are uncorrelated and occur in directions with strong selection and high genetic variation (Chevin 2013).	Strong plasticity increases extinction risk if environmental cues are unreliable (Reed et al. 2010). Predictable fluctuations can select for increased plasticity.
Spatial Heterogeneity			
	Spatial heterogeneity constrains adaptation. Trait interactions can induce "counter-gradient" clines, causing traits to evolve away from the optimum (Duputié et al. 2012).	Population growth is maximized at intermediate dispersal rates. Critical rate of environmental change increases if spatial selection gradient is aligned with direction of abundant genetic variation and weak stabilizing selection (Duputié et al. 2012).	If plasticity is expressed before (after) migration, it increases (reduces) migration load and can decreases (increase) species ranges. Expressed plasticity increases near range limits (Chevin and Lande 2011; Thibert-Plante and Hendry 2011).

Table 1 – A summary of theoretical predictions for models of adaptation to environmental change.

8. Appendix

Appendix 1: Adaptation and extinction in the one-dimensional moving-optimum model

The following is a simplified version of the model by Bürger and Lynch (1995), which assumes the Gaussian fitness function

$$w_{z,t} = B \exp\left(-\frac{(z-\theta_t)^2}{2\omega^2}\right) \quad \text{with} \tag{A1}$$

$$\theta_t = kt \tag{A2}$$

Here, z is the phenotype of an individual, $w_{z,t}$ its fitness at time t, θ_t is the optimal phenotype, which increases linearly at rate k, and ω^2 measures the width of the fitness landscape (i.e., selection is strong if ω^2 is small). B is the expected number of offspring (absolute fitness) of a perfectly adapted individual, and hence $\ln B$ is the maximal population growth rate.

If the trait z is normally distributed in the population with mean $\bar{z}_t$ and variance σ_p^2, the mean absolute fitness at time t is

$$\bar{w}_t = B\sqrt{\frac{\omega^2}{\sigma_g^2 + V_s}} \exp\left(-\frac{(\bar{z}_t-\theta_t)^2}{2(\sigma_g^2+V_s)}\right), \tag{A3}$$

with $V_s = \omega^2 + \sigma_e^2$ describing the effective width of the fitness landscape (which is somewhat "smeared out" by the environmental variance σ_e^2). Equation (A3) shows that the maximal fitness B is reduced by two components of *genetic load*: The *standing load* (the square root term) due to standing genetic variation, and the *lag load* due to the deviation of the mean phenotype from the optimum.

For constant σ_g^2, a population with mean phenotype $\bar{z}_t$ evolves according to Lande's equation $\Delta\bar{z}_t = \sigma_g^2\beta_t$, where the directional selection gradient at time t is

$$\beta_t = \frac{d\ln\bar{w}_t}{d\bar{z}_t} = \frac{\theta_t - \bar{z}_t}{\sigma_g^2 + V_s}. \tag{A4}$$

β_t measures the proportional change in log mean fitness per unit change of the mean phenotype. As outlined in the main text, the population will reach a state of dynamic equilibrium, where it follows the optimum with a constant lag, which is given by

$$\delta_t^* = kt - \bar{z}_t = k\frac{\sigma_g^2 + V_s}{\sigma_g^2} \tag{A5}$$

(Bürger and Lynch 1995).

At the same time, the population dynamics are governed by $N_{t+1} = N_t\bar{w}_t$ (e.g., Gomulkiewicz and Holt 1995) or a density-dependent version thereof (e.g., Bürger and Lynch 1995). In any case, population survival requires that, given the equilibrium lag δ_t^*, the equilibrium mean fitness $\bar{w}^* \geq 1$. This condition yields the critical rate of environmental change

$$k_{\text{crit}} = \sigma_g^2\sqrt{\frac{2\ln\left(B\sqrt{\frac{\omega^2}{\sigma_g^2+V_s}}\right)}{\sigma_g^2+V_s}} \approx \sigma_g^2\sqrt{\frac{2\ln B}{V_s}}, \tag{A6}$$

(Bürger 2000), where the approximation is valid for weak selection ($V_s \geq 20$; see Bürger 2000). When scaled by the phenotypic standard deviation, eq. (A6) gives the critical rate of phenotypic evolution

$$\kappa_{\text{crit}} = k_{\text{crit}}/\sigma_p \tag{A7}$$

in *haldanes*. Figure 3 illustrates the value of κ_{crit} as a function of heritability, the width of the fitness landscape and the reproductive potential of the population. The rule of thumb $\kappa_{\text{crit}} \leq 0.1$ (Bürger and Lynch 1995) is based on V_s between 5 and 100, $\ln(B) < 1$, and $h^2 < 0.5$. Bürger and Lynch (1995) note that genetic drift and fluctuating selection might decrease κ_{crit} even further.

Appendix 2: Adaptation and extinction in the multi-dimensional moving-optimum model

The multivariate version of model (A2) for n selected traits is

$$w_{\mathbf{z},t} = B\exp\left(-\frac{1}{2}(\mathbf{z}-\boldsymbol{\theta}_t)^T\boldsymbol{\omega}^{-1}(\mathbf{z}-\boldsymbol{\theta}_t)\right). \tag{A8}$$

where the fitness landscape is a bell-shaped "hill", whose orientation and dimensions are determined by the (positive semi-definite) covariance matrix $\boldsymbol{\omega}$ (of size $n \times n$).

If the phenotype distribution is multivariate normal, the mean fitness is

$$\bar{w}_t = B\sqrt{\det((\boldsymbol{\omega}+\mathbf{P})^{-1}\boldsymbol{\omega})}\exp\left(-\frac{1}{2}(\bar{\mathbf{z}}_t-\boldsymbol{\theta}_t)^T(\boldsymbol{\omega}+\mathbf{P})^{-1}(\bar{\mathbf{z}}_t-\boldsymbol{\theta}_t)\right), \tag{A9}$$

which, as in the univariate case, is reduced by a standing load (the square root term) and a lag load (the exponential).

The mean phenotype evolves according to the multivariate Lande equation $\Delta\bar{\mathbf{z}}_t = \mathbf{G}\boldsymbol{\beta}_t$, where the multivariate selection gradient is

$$\boldsymbol{\beta}_t = (\boldsymbol{\omega} + \mathbf{P})^{-1}(\boldsymbol{\theta}_t - \bar{\mathbf{z}}_t) \tag{A10}$$

In the gradual-change scenario, $\boldsymbol{\theta}_t = \mathbf{k}t$, the rate and the direction of environmental change is described by a speed vector $\mathbf{k} = (k_1, \ldots, k_n)'$, which contains the rates of change in the optimum for each trait. As in the univariate case, the population will eventually follow the optimum with a constant lag (assuming the **G**-matrix is constant):

$$\boldsymbol{\delta}_t^* = (\boldsymbol{\omega} + \mathbf{P})\mathbf{G}^{-1}\mathbf{k}$$

(Jones et al. 2004; Gomulkiewicz and Houle 2009; Chevin 2013; Jones et al. 2012). Again, the population can persist if $\bar{w}^* \geq 1$. If the vector **k** is decomposed into its length and its direction, $\mathbf{k} = ||\mathbf{k}||\mathbf{c}$ with $\mathbf{c} = \mathbf{k}/||\mathbf{k}||$, then this condition is satisfied if

$$||\mathbf{k}|| \geq \sqrt{\frac{2\ln(B) + \ln(\det((\boldsymbol{\omega} + \mathbf{P})^{-1}\boldsymbol{\omega}))}{\mathbf{c}^T\mathbf{G}^{-1}(\boldsymbol{\omega} + \mathbf{P})\mathbf{G}^{-1}\mathbf{c}}} \tag{A11}$$

(Gomulkiewicz and Houle 2009).

Appendix 3: Fixation of a major mutation

Assume constant selection and a major mutation increasing fitness from $1 - s$ to 1. Let the phenotypic effect of this mutation be δz. For simplicity, we look at the haploid case and neglect genetic variation at other loci as well as environmental variance. Then, the phenotypic variance of the population at time t is $\sigma_{p,t}^2 = p_t(1 - p_t)\delta z^2$, where p_t is the frequency of the beneficial allele. The per generation change in mean phenotype is

$$\Delta\bar{z}_t = \delta z p_t(1 - p_t)\frac{s}{1 - s + sp_t}, \tag{A12}$$

which in *haldanes* is

$$\frac{\Delta z_t}{\sigma_{p,t}} = \sqrt{p_t(1 - p_t)}\frac{s}{1 - s + sp_t}, \tag{A13}$$

independent of δz. The maximal rate of change, which is achieved when $p = 1/2$, is $s/(2 - s)$,

which may be large if selection is strong (e.g., for $s = 1/2$, $\kappa_{\max} = 1/2$).

Appendix 4: Maximal sustainable rates of phenotypic evolution over "time frames of conservation interest"

Barrett and Hendry (2012) have argued that, over time frames of conservation interest, maximal sustainable rates of phenotypic evolution could well exceed the 0.1 *haldanes* that have been proposed by Bürger and Lynch (1995) for the long-term equilibrium of the moving-optimum model. Their point was that environments will not keep changing forever, and that conservation biology is rather concerned with population survival over modest periods of time (e.g., 50 generations). Here, we attempt to evaluate this claim by calculating critical rates of environmental and phenotypic change, $k_{\text{crit}}(t_{\text{crit}}, N_{\text{crit}})$ and $\kappa_{\text{crit}}(t_{\text{crit}}, N_{\text{crit}})$, such that the population consists of N_{crit} individuals after t_{crit} generations. Note that, since we are no longer considering a dynamic equilibrium, the two rates k_{crit} and κ_{crit} are no longer equivalent. Our analysis is based on a "quasi-deterministic" approximation developed by Bürger and Lynch (1995) for studying the mean time to extinction. This analysis neglects evolution of genetic variance in response to selection, as well as several sources of stochasticity (see Appendix 5). Its results can, therefore, only be a first approximation, which however, help to elucidate several principals.

Consider, first, the case $N_{\text{crit}} = N_0$, that is, we require that the population size does not decline from its initial value N_0 over t_{crit} generations. The corresponding critical rate of environmental change can be calculated by rearranging equation (12a) in Bürger and Lynch (1995), which gives

$$k_{\text{crit}}(t_{\text{crit}}, N_0) = k_{\text{crit}}(\infty, N_0)\left(1 - \exp\left[-\frac{\sigma_g^2 + V_s}{\sigma_g^2} t_{crit}\right]\right)^{-1}, \tag{A14}$$

where $k_{\text{crit}}(\infty, N_0)$ is the critical rate given in equation (A6) for infinite times. While $k_{\text{crit}}(t_{\text{crit}}, N_0)$ can substantially exceed $k_{\text{crit}}(\infty, N_0)$, the corresponding critical rates of phenotypic change are identical, that is, $\kappa_{\text{crit}}(t_{\text{crit}}, N_0) = \kappa_{\text{crit}}(\infty, N_0) = k_{\text{crit}}(\infty, N_0)/\sigma_p$. The reason is that both $\kappa_{\text{crit}}(t_{\text{crit}}, N_0)$ and $\kappa_{\text{crit}}(\infty, N_0)$ are achieved when the mean absolute fitness $\bar{w} = 1$ (see eq. A3). This illustrates that equation (A6) does not depend on the assumption of an indefinitely moving optimum, and that the corresponding κ_{crit} simply gives the maximal rate at which the population can evolve without decreasing in size. In

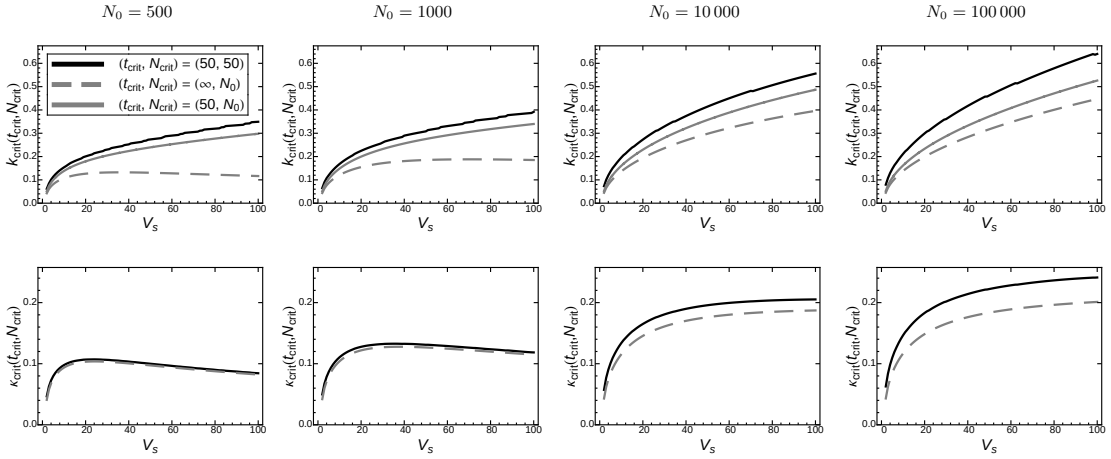

Figure A1 – Critical rates of environmental change k_{crit} (top row) and the corresponding rates of phenotypic evolution κ_{crit} (bottom row), under the premise that the population maintains a minimal size of N_{crit} individuals over t_{crit} generations. The case $t_{crit} = \infty, N_{crit} = N_0$ (where N_0 is the initial population size, which equals the carrying capacity; black line) corresponds to the case investigated by Bürger and Lynch (1995). The case $t_{crit} = 50, N_{crit} = N_0$ (grey line) is given by equation A14. In the bottom row, red and grey lines are identical, because $\kappa_{crit}(t_{crit}, N_0) = \kappa_{crit}(\infty, N_0)$. Parameters are as in the bottom row of Fig. 3 with $B = 2$.

other words, rates of phenotypic evolution can only exceed $\kappa_{crit}(\infty, N_0)$ if population size declines.

To study this case, we now allow moderate population decline while still requiring the population size to remain above a critical threshold $N_{crit} < N_0$ over t_{crit} generations. No analytical solution exists (Bürger and Lynch 1995), but the critical rates can be estimated numerically by iterating equation (2.4). Since a reduction in population size also entails a reduced genetic variance, we followed Bürger and Lynch (1995) by assuming that σ_g^2 at any time is given by the stochastic house-of-cards approximation for the current N.

Figure A1 shows maximal rates of environmental and phenotypic change under the constraint that the population is to maintain a minimal size of $N_{crit} = 50$ individuals over $t_{crit} = 50$ generations, and compares the results to those from the Bürger and Lynch (1995) framework (no reduction in population size over infinite times) and those from equation (A14) (no reduction in population size over 50 generations). The critical rate of environmental change, k_{crit} increases substantially when short-term reductions in population size are allowed (top row of Figure A1). In contrast, the differences in the critical rates of phenotypic change, κ_{crit} are much less pronounced (bottom row), in particular for small populations (which might be of highest interest for conservation). Even in large populations, the relative increase in κ_{crit} rarely exceeds 30% (unless selection is

extremely strong). Given the large uncertainty in our estimates of evolutionary rates (see below), this increase appears minor, and we conclude that considering adaptation over "time-frames of conservation interest" does not substantially alter the rule-of-thumb that critical rates are typically around 0.1 *haldanes*.

Appendix 5: Stochastic fluctuations in evolutionary rates

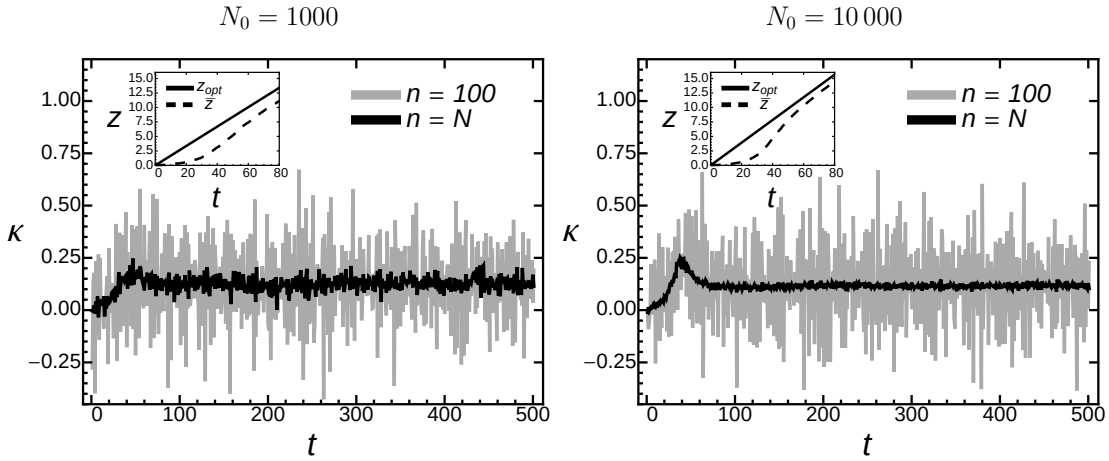

Figure A2 – Observed generation-to-generation rates of phenotypic change κ in *haldanes* for the entire population ($n = N$, red line) or based on a sample of $n = 100$ individuals (grey line), for two simulation runs with carrying capacities (and initial population sizes) $N_0 = 1000$ and $N_0 = 10000$, respectively, and parameters as in Fig. A1. The inset shows the trajectories of the mean phenotype $\bar{z}$ and the phenotypic optimum z_{opt}. The spike in κ around generation 40, which partially closes the large initial phenotypic lag (insert), is due to an increase in genetic variance (see main text). Fluctuations in the red line reflect genetic drift and environmental variance, whereas those in the grey line are largely due to sampling effects. In addition, rates measured in *haldanes* vary due to fluctuations in the phenotypic variance σ_p^2 (for potential problems of scale, see Hereford et al. 2004; Hansen and Houle 2008).

The analysis presented in Appendix 4 was based on a deterministic approximation, which neglects various sources of stochasticity (see main text). To illustrate this stochasticity, we conducted individual-based simulations as described in Bürger and Lynch (1995). Two exemplary runs are shown in Figure A2. While the population mean phenotype follows the moving optimum, generation-to-generation rates of phenotypic change (κ) in *haldanes* fluctuate as a consequence of non-selective factors such as genetic drift, environmental variance and fluctuations in the phenotypic variance σ_p^2. Observed fluctuations in κ are further amplified if only a part of the population is sampled (grey lines in Fig. A2), and their range can largely surpass the 0.1 *haldanes* predicted by Bürger and Lynch (1995), see Figure A3. Similarly, in small populations, drift and environmental variance alone can induce rates of changes of up to 0.15 *haldanes* (Fig. A4). Overall,

these results cast serious doubt on our ability to predict the fate of populations based on short-term measures of micro-evolutionary change.

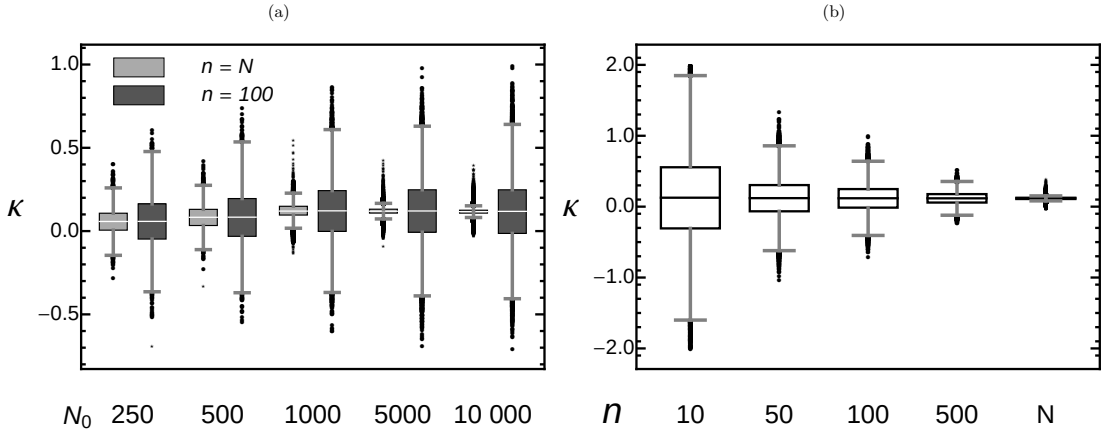

Figure A3 – Distribution of observed generation-to-generation rates of phenotypic change κ in *haldanes*, over 100 simulation runs similar to those in Fig. A2. In (a), rates based on the entire population ($n = N$) or on samples of size $n = 100$ are shown for various initial population sizes (and carrying capacities) N_0. In (b), $N_0 = 10000$ was kept constant and only sample size n was varied. Other parameters are as in Fig. A1.

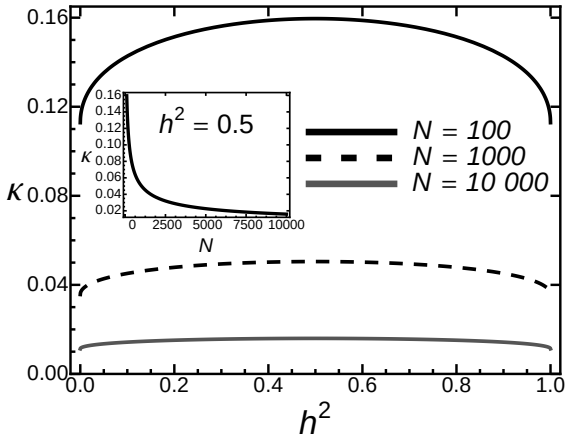

Figure A4 – Expected absolute rate of phenotypic change κ between generations due to genetic drift and environmental variance, which contribute $2\sqrt{h^2/(\pi N_e)}$ and $2\sqrt{(1-h^2)/(\pi N)}$, respectively (see main text), as a function of heritability h^2 and population size $N = N_e$ (inset). Environmental variance σ_e^2 refers to the phenotypic variance caused by developmental instability and micro-environmental fluctuations.

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Information about submission and S. Matuszewski's contribution

STATUS:	published
JOURNAL:	Evolutionary Applications 7(1):169-191
DATE OF ACCEPTANCE:	26.09.2013

S. MATUSZEWSKI'S CONTRIBUTION: Contributed to the model design, derived the numerical and the analytical results, wrote simulation code and the manuscript draft.

Fisher's geometric model with a moving optimum

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ABSTRACT. *Fisher's geometric model has been widely used to study the effects of pleiotropy and organismic complexity on phenotypic adaptation. Here, we study a version of Fisher's model in which a population adapts to a gradually moving optimum. Key parameters are the rate of environmental change, the dimensionality of phenotype space, and the patterns of mutational and selectional correlations. We focus on the distribution of adaptive substitutions, that is, the multivariate distribution of the phenotypic effects of fixed beneficial mutations. Our main results are based on an "adaptive-walk approximation", which is checked against individual-based simulations. We find that (i) the distribution of adaptive substitutions is strongly affected by the ecological dynamics and largely depends on a single composite parameter γ, which scales the rate of environmental change by the "adaptive potential" of the population; (ii) the distribution of adaptive substitution reflects the shape of the fitness landscape if the environment changes slowly, whereas it mirrors the distribution of new mutations if the environment changes fast; (iii) in contrast to classical models of adaptation assuming a constant optimum, with a moving optimum, more complex organisms evolve via larger adaptive steps.*

1. Introduction

Natural populations are constantly faced with environmental changes that force them to either adapt or go extinct. In *Arabidopsis thaliana*, Hancock et al. (2011) recently identified candidate SNPs scattered over the entire genome that affect flowering time and vernalization and are strongly correlated with climate variables. Likewise, annual cycles of reproduction of various plants and animals have been adjusted to the peak availability of food as a response to changing environments (Gienapp et al. 2013). Conversely, migratory bird species that fail to respond phenologically decline in population size (Møller et al. 2008). The brood parasitic common cuckoo (*Cuculus canorus*) population, for example, declined in size by 6% since 1980, as they failed to synchronize their reproductive and migratory cycles with those of their particular host species, to which they are adapted to in terms of egg size, coloration and spottiness (Antonov et al. 2010; Møller et al. 2011).

In recent years, numerous theoretical studies of the population genetics of adaptation have attempted to provide a formal framework for the observed empirical phenomena (for a review see Orr 2005b). Central to these studies is the description of the fundamental

event during adaptation, that is, the substitution of a resident allele (i.e. gene variant) by a beneficial mutation. The statistical description of this process has been at the heart of evolutionary biology (Charlesworth 1996), and is key to addressing seemingly simple questions, such as: From the set of mutations that emerge in a population, which are the ones that will get fixed and what is their effect on phenotype or fitness? Will adaptation proceed by many steps of small effect or just by a few adaptive substitutions of large effect? Do simple organisms evolve faster than complex ones?

One of the most influential models of adaptive phenotypic evolution is Fisher's geometric model (FGM) (Fisher 1930). In this model, a phenotype is treated as a point in a multidimensional trait space, and mutations are random vectors in this space, which are beneficial if they bring the mutant phenotype closer to a nearby local optimum. Thus, FGM implicitly assumes "universal pleiotropy" (each mutation affects every trait) and, therefore, equates pleiotropy with "organismic complexity". Despite its simplicity and the lack of a clear genetic context (Chevin et al. 2010), FGM, more than 80 years after its proposal, has yielded several robust predictions supported by growing empirical evidence: First, the distribution of fitness effects of new mutations is well approximated by a (displaced) negative gamma distribution (Martin and Lenormand 2006a; for empirical support see Hietpas et al. 2013). Second, the distribution of adaptive substitutions is approximately exponential, meaning that most fixed mutations are of small and only a few are of large effect (Orr 1998; for empirical support see Rockman 2012, but see Bell 2009). Finally, fixed mutational effects become on average smaller as organismic complexity increases (Orr 2000; for empirical support see Cooper et al. 2007) – a phenomenon that has been termed "the cost of complexity" (Orr 2000; Welch and Waxman 2003; Wagner and Zhang 2011).

The classical version of FGM, however, only addresses the situation where a population is confronted with constant stabilizing selection after a sudden change in the environment (e.g., Orr 2002; Martin and Lenormand 2006a). In nature, in contrast, environmental change may as often be gradual (Hairston et al. 2005; Thompson 2005; Parmesan 2006; Perron et al. 2008). Collins (2011b) recently emphasized that "using [models of] instantaneous environmental change to understand adaptive evolutionary responses to gradual change will not only underestimate the amount of adaptation, but also predict the wrong genotypic and phenotypic changes." Indeed, the necessity to include gradual environmental change into studies of adaptive evolution has long been recognized in quantitative genetics (e.g., Maynard Smith 1976). A number of studies have focused on the so-called moving-optimum model, in which the optimal values of a quantitative trait change over time (Lynch and Lande 1993; Bürger and Lynch 1995; Waxman

and Peck 1999; Bürger and Gimelfarb 2002; Nunney 2003; Collins et al. 2007; Gordo and Campos 2013); extensions include multivariate phenotypes and the effects of pleiotropic constraints (Jones et al. 2004; Gomulkiewicz and Houle 2009; Jones et al. 2012; Chevin 2013; Lourenco et al. 2013). The focus of these studies was, however, on the rate of adaptation (Lynch and Lande 1993; Bürger and Lynch 1995; Gomulkiewicz and Holt 1995; Nunney 2003; Hansen and Houle 2008; Chevin 2013; Kopp and Matuszewski 2014) and the evolution and maintenance of genetic variation (Bürger 1999; Waxman and Peck 1999; Bürger and Gimelfarb 2002; Gomulkiewicz and Houle 2009; Jones et al. 2004, 2012). In contrast, characteristics of individual substitutions have been addressed only recently (Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b). In particular, Kopp and Hermisson (2007, 2009a) employed the moving-optimum model of a single quantitative trait to study the fixation time of single mutations and the order in which mutations of different phenotypic effect sizes become fixed. Their latest study (Kopp and Hermisson 2009b) addresses the distribution of adaptive substitutions during long-term adaptation. Specifically, they showed that this distribution is almost entirely determined by a scaled rate of environmental change γ, which combines ecological and genetic factors (see below), and is unimodal (with an intermediate mode) rather than exponential. That is, most substitutions have an intermediate phenotypic effect, while small- and large-effect substitutions are rare.

An obvious next question is how these results are affected if phenotypic adaptation to gradual change is constrained by pleiotropic correlations among the traits under selection (as frequently observed in nature; Svensson et al. 2001; Roff and Fairbairn 2012; Guerreiro et al. 2012). This is the aim of the present article. This way, we integrate two modelling traditions, which have had little overlap so far: on the one hand, the multivariate moving-optimum model as used by Jones et al. (2004, 2012), and on the other hand, Fisher's classical geometric model for the study of adaptive effect sizes (Fisher 1930; Orr 1998, 2000). We study how the expected distribution of adaptive steps is influenced by the rate of environmental change, the number of traits under selection (i.e., "organismic complexity") and by selectional and mutational correlations (i.e., the shapes of the fitness landscape and the multivariate distribution of new mutations). Our analysis shows that the genetic basis of adaptation crucially depends on the tempo and mode of environmental change.

2. Model and Methods

2.1. Model description

Phenotype, environmental change and selection. We consider the evolution of n phenotypic traits $\mathbf{z} = (z_1, \ldots, z_n)'$, each of which is under Gaussian stabilizing selection with regard to a time-dependent optimum $\mathbf{z}_{\text{opt}}(t)$:

$$w(\mathbf{z}, t) = \exp\left[-\left(\mathbf{z} - \mathbf{z}_{\text{opt}}(t)\right)' \boldsymbol{\Sigma}^{-1} \left(\mathbf{z} - \mathbf{z}_{\text{opt}}(t)\right)\right]. \tag{1}$$

where $'$ denotes transposition and $\boldsymbol{\Sigma}$ (and thus also $\boldsymbol{\Sigma}^{-1}$) is an $n \times n$ positive definite and symmetric matrix. Throughout this paper, we choose the linearly moving optimum,

$$\mathbf{z}_{\text{opt}}(t) = \mathbf{v}t, \tag{2}$$

where $\mathbf{v} = (v_1, \ldots, v_n)'$ is the vector of environmental change. In the following, we will interchangeably refer to n as the "degree of pleiotropy" or the "degree of complexity".

The matrix $\boldsymbol{\Sigma}$ describes the shape of the fitness landscape (including a contribution of environmental noise to the phenotype $\mathbf{z}$, which otherwise is not modeled explicitly; see Bürger 2000). We will say that selection is isotropic if $\boldsymbol{\Sigma}$ is proportional to an identity matrix, $\boldsymbol{\Sigma} = \sigma^2\mathbf{I}$ ($\sigma^2 > 0$); and selection is correlated if $\boldsymbol{\Sigma}$ has non-zero off-diagonal entries. As a measure for the average width of the fitness landscape, we define

$$\bar{\sigma}^2 = \sqrt[n]{\det(\boldsymbol{\Sigma})}, \tag{3}$$

which is the geometric mean of the eigenvalues of $\boldsymbol{\Sigma}$ (if the fitness landscape is represented by an ellipse, as in Fig. S1_1 below, the axes of the ellipse have length proportional to the square root of the eigenvalues). Note that overall selection is strong if $\bar{\sigma}^2$ is small.

Genotypes and mutation. In accordance with Fisher's original model, we make the assumption of "universal pleiotropy", that is, each mutation affects every trait. We denote by $\boldsymbol{\alpha}$ the vector of the phenotypic effects of a mutation, and we assume that its distribution $p(\boldsymbol{\alpha})$ (which we will refer to as the distribution of new mutations) is multivariate normal with mean $\mathbf{0}$ and covariance matrix $\mathbf{M}$ (thus, we assume a continuum-of-alleles model), that is

$$p(\boldsymbol{\alpha}) = \frac{1}{\sqrt{2\pi^n \det(\mathbf{M})}} \exp\left(-\frac{1}{2}\boldsymbol{\alpha}'\mathbf{M}^{-1}\boldsymbol{\alpha}\right). \tag{4}$$

Like $\mathbf{\Sigma}$, $\mathbf{M}$ has dimensions $n \times n$ and must be symmetric and positive definite. The diagonal elements of $\mathbf{M}$ are the variances of the mutational effects for individual traits, whereas off-diagonal elements are the mutational covariances. We will say that mutation is isotropic if $\mathbf{M}$ is proportional to an identity matrix, $\mathbf{M} = m^2\mathbf{I}$ ($m^2 > 0$); and mutation is correlated if $\mathbf{M}$ has non-zero off-diagonal entries. A measure for the average variance of mutational effects (in an arbitrary direction) is given by

$$\bar{m}^2 = \sqrt[n]{\det(\mathbf{M})}. \tag{5}$$

When comparing different degrees of pleiotropy/complexity, we typically assume that the distribution of mutational effects on a given trait is independent of the total number of traits n (so-called Euclidean superposition model; Turelli 1985; Wagner 1988; Wagner and Zhang 2011). For example, with isotropic mutation (see above), adding more traits does not change the parameter $\bar{m}^2$. As a consequence, the average *total* effect of a mutation increases with n.

In Supporting Information 2, we introduce a transformation that shows that the general model outlined above can always be reduced to a model with isotropic selection ($\mathbf{\Sigma} = \sigma^2\mathbf{I}$) and movement of the optimum along a single dimension ($\mathbf{v} = (v_1, 0, \ldots, 0)'$). In this transformed phenotype space, the effects of selectional and mutational correlations are entirely captured by the $\mathbf{M}$-matrix (and, in particular, the orientation of its leading eigenvector/first principal component) relative to the direction of environmental change. Furthermore, all vectors (e.g., $\mathbf{z}, \mathbf{v}, \boldsymbol{\alpha}$) are measured relative to the average width of the distribution of new mutations $\bar{m}$.

2.2. The adaptive-walk approximation

The aim of this article is to investigate the distribution of adaptive substitutions $\phi(\boldsymbol{\alpha})$, that is, the distribution of the effects of those mutations that eventually go to fixation and contribute to adaptation. Our main analytical tool will be the "adaptive-walk approximation". Following Kopp and Hermisson (2009b), this approximation is based on the simplifying assumption that whether a new beneficial mutation goes to fixation or is lost by drift is determined immediately after its appearance and that, in the former case, fixation occurs instantaneously. Therefore, the population can be considered monomorphic nearly all of the time, and adaptation occurs as a series of discrete "steps", which together will be referred to as an "adaptive walk" (Kauffman 1993; Orr 2000). This approximation ignores interactions between co-segregating mutations, such as epistasis, linkage and Hill-Robertson interference (Hill and Robertson 1966).

Adaptive walks can easily be simulated using the following algorithm: (i) draw the waiting time for a new mutation from an exponential distribution with parameter $\Theta/2$ (where Θ is a standard measure for the population- and genomewide mutation rate); (ii) draw the size of the mutation from its distribution $p(\boldsymbol{\alpha})$ (eq. 4); (iii) accept the mutation (i.e., perform an adaptive step) with its fixation probability

$$p_{\text{fix}}(\mathbf{x}, \mathbf{y}, t) \approx \begin{cases} 2s(\mathbf{x}, \mathbf{y}, t) & \text{for } s(\mathbf{x}, \mathbf{y}, t) > 0 \\ 0 & \text{for } s(\mathbf{x}, \mathbf{y}, t) \leq 0 \end{cases} \tag{6}$$

(Haldane 1927), where $\mathbf{y}$ is the current population phenotype, $\mathbf{x} = \mathbf{y} + \boldsymbol{\alpha}$ is the mutant phenotype, and

$$s(\mathbf{x}, \mathbf{y}, t) = \frac{w(\mathbf{x}, t)}{w(\mathbf{y}, t)} - 1 \tag{7}$$

denotes the selection coefficient of the mutant $\mathbf{x}$ in a wild-type population with phenotype $\mathbf{y}$ at time t. Note that equation (6) assumes s to be small and neglects chance fixations of deleterious mutations. In some simulations, we also used the slightly more accurate approximation $p_{\text{fix}} \approx \max(0, 1 - \exp(-2s))$. (Even more accurate approximations exist that account for the change in the selection coefficient during the fixation process due to the environmental change, see Uecker and Hermisson 2011; however, within the simple framework of the adaptive walk model we do not obtain further improvement.)

2.2.1. The distribution of adaptive substitutions

In the following we derive an analytical expression for the distribution $\phi(\boldsymbol{\alpha}|\mathbf{y})$ of the size $\boldsymbol{\alpha} = \mathbf{x} - \mathbf{y}$ of the next adaptive substitution given an initial phenotype $\mathbf{y}$ at time $t = 0$. First, equation 7 can be approximated by

$$\begin{aligned} s(\mathbf{x}, \mathbf{y}, t) &\approx (\mathbf{y} - \mathbf{v}t)' \boldsymbol{\Sigma}^{-1} (\mathbf{y} - \mathbf{v}t) - (\mathbf{x} - \mathbf{v}t)' \boldsymbol{\Sigma}^{-1} (\mathbf{x} - \mathbf{v}t) \\ &= \lambda_{\mathbf{x},\mathbf{y}} \left(t - \tau_{\mathbf{x},\mathbf{y}} \right), \end{aligned} \tag{8a}$$

with

$$\lambda_{\mathbf{x},\mathbf{y}} = 2(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} \mathbf{v} \tag{8b}$$

$$\tau_{\mathbf{x},\mathbf{y}} = \frac{(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} (\mathbf{x} + \mathbf{y})}{2(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} \mathbf{v}} \tag{8c}$$

(provided $\lambda_{\mathbf{x},\mathbf{y}} \neq 0$). That is, with a linearly moving optimum, the selection coefficient increases or decreases approximately linearly over time, where $\lambda_{\mathbf{x},\mathbf{y}}$ is the rate of change and $\tau_{\mathbf{x},\mathbf{y}}$ is the time when s reaches zero (the "lag time" in the terminology of Kopp and

Hermisson 2007). This time dependence of the selection coefficient is illustrated in Supporting Information 1. The distribution $\phi(\boldsymbol{\alpha}|\mathbf{y})$ can then be calculated in four steps.

The instantaneous rate of substitutions. We denote by $g(t, \mathbf{y})$ the rate at which substitutions of any kind happen at time t. $g(t, \mathbf{y})$ is given by

$$g(t, \mathbf{y}) = \Theta \int_{\chi(t,\mathbf{y})} p(\mathbf{x} - \mathbf{y}) s(\mathbf{x}, \mathbf{y}, t) d\mathbf{x}. \tag{9}$$

where $\chi(t, \mathbf{y}) = \{\mathbf{x} \mid s(\mathbf{x}, \mathbf{y}, t) > 0\}$ is the set of all mutant phenotypes with positive selection coefficient at time t. The integrand in (9) is simply the product of the probability that a mutation with phenotype $\mathbf{x}$ arises ($\Theta p(\boldsymbol{\alpha})/2$) and its probability of fixation approximated as ($2s(\mathbf{x}, \mathbf{y}, t)$, see eq. 6).

The waiting-time distribution. We denote by $F(t|\mathbf{y})$ the probability that no fixation has happened before time t (thus, $1 - F(t|\mathbf{y})$ is the cumulative distribution function of the waiting time to the next fixation). From the theory of Poisson processes,

$$F(t|\mathbf{y}) = \exp\left(- \int_0^t g(\tau, \mathbf{y}) d\tau \right). \tag{10}$$

The conditional distribution of step sizes. The distribution of step sizes, given that the step occurs at time t, is simply proportional to the distribution of new mutations weighted by the selection coefficient (Gillespie 1983; Kopp and Hermisson 2009b):

$$\phi(\boldsymbol{\alpha}|t, \mathbf{y}) = \begin{cases} \frac{\Theta p(\boldsymbol{\alpha}) s(\mathbf{y}+\boldsymbol{\alpha}, \mathbf{y}, t)}{g(t, \mathbf{y})} & \text{if } s > 0 \\ 0 & \text{otherwise.} \end{cases} \tag{11}$$

The distribution of step sizes. Finally, the unconditional distribution of the size of the next adaptive step can be calculated by integrating over all possible waiting times (see Kopp and Hermisson 2009b), yielding

$$\phi(\boldsymbol{\alpha}|\mathbf{y}) = \int_0^\infty \phi(\boldsymbol{\alpha}|t, \mathbf{y}) f(t|\mathbf{y}) dt, \tag{12a}$$

where $f(t|\mathbf{y}) = (1 - F(t|\mathbf{y}))'$ is the density of the waiting-time distribution. Equation (12a) can also be written as

$$\phi(\boldsymbol{\alpha}|\mathbf{y}) = \begin{cases} \Theta \int_{\max(0,\tau_{\mathbf{x},\mathbf{y}})}^{\infty} p(\boldsymbol{\alpha}) s\left(\mathbf{x},\mathbf{y},t\right) F(t|\mathbf{y}) dt & \text{if } \lambda_{\mathbf{x},\mathbf{y}} \geq 0 \\ \Theta \int_{0}^{\max(0,\tau_{\mathbf{x},\mathbf{y}})} p(\boldsymbol{\alpha}) s\left(\mathbf{x},\mathbf{y},t\right) F(t|\mathbf{y}) dt & \text{if } \lambda_{\mathbf{x},\mathbf{y}} < 0 \end{cases} \tag{12b}$$

where $\tau_{\mathbf{x},\mathbf{y}}$ is given by equation (8c).

2.2.2. The parameter γ

Supporting Information 3 shows that the distribution of step sizes in the adaptive-walk approximation depends only on the distribution of new mutations and the composite parameter

$$\gamma = \frac{\sqrt{\mathbf{v}'\boldsymbol{\Sigma}^{-1}\mathbf{v}}}{\Theta\left(\bar{\sigma}/\bar{m}\right)^{-3/2}} \tag{13}$$

where the term in the numerator can be interpreted as the rate of environmental change relative to the width of the fitness landscape in the direction of the moving optimum. If selection is isotropic, equation (13) reduces to

$$\gamma = \frac{\frac{\|\mathbf{v}\|}{\bar{m}}}{\Theta\left(\bar{\sigma}/\bar{m}\right)^{-2}}, \tag{14}$$

which is equivalent to the γ defined by Kopp and Hermisson (2009b) for the single-trait case, except for differences in notation, and is independent of n. Here, $\bar{\sigma}/\bar{m}$ describes the mean width of the fitness landscape relative to the mean effect size of new mutations, and $(\bar{\sigma}/\bar{m})^{-2}$ can be seen as a scale-free measure for the strength of stabilizing selection. The product of this term and the population-wide mutation rate Θ determines the "adaptive potential" of the population, γ can, thus, be interpreted as a scaled rate of environmental change (how fast the population needs to adapt relative to how readily it can adapt). In particular, it can be used to distinguish two limiting cases (Kopp and Hermisson 2009b). If γ is small, the population can easily follow the optimum. The adaptive process is, therefore, *environmentally-limited*, and the distribution of adaptive substitutions is primarily determined by the lag time $\tau_{\mathbf{x},\mathbf{y}}$, which determines when a mutation of effect $\boldsymbol{\alpha} = \mathbf{x}-\mathbf{y}$ becomes beneficial ("dynamic sieve" *sensu* Kopp and Hermisson 2009b). If γ is large, the population will follow the optimum with a large lag. In this case, the adaptive process is *genetically-limited*, and the distribution of adaptive substitutions is largely determined by the distribution of new mutations $p(\boldsymbol{\alpha})$ ("static sieve" *sensu* Kopp and Hermisson 2009b). Numerical values for γ in these two regimes are discussed in Supporting Information 3.

2.2.3. The environmentally-limited regime

In the environmentally-limited regime, the Gaussian distribution of new mutations, $p(\boldsymbol{\alpha})$, can be approximated by a uniform distribution $p_u(\boldsymbol{\alpha})$ with the same density at $\boldsymbol{\alpha} = 0$, that is,

$$p_0 = p_u(\boldsymbol{\alpha}) = p(\mathbf{0}) = \left(\frac{1}{\sqrt{2\pi\bar{m}^2}}\right)^n \tag{15}$$

(see Kopp and Hermisson 2009b). This approximation is justified if the optimum moves so slowly that all beneficial mutations are small ($\boldsymbol{\alpha}$ close to $\mathbf{0}$). It allows to directly calculate several properties of the distribution of adaptive substitutions. In particular, if the wild-type phenotype $\mathbf{y} = \mathbf{0}$ (i.e., the population is perfectly adapted at time $t = 0$), the distribution of the "first" substitution (and all its moments) can be calculated analytically (Supporting Information 4).

2.3. Individual-based simulations

In addition to our adaptive-walk approximation, we conducted individual-based simulations (implemented in C++, available upon request; see Bürger 2000; Kopp and Hermisson 2009b), which allow multiple mutations to segregate simultaneously, while making additional assumptions about the genetic architecture of the selected traits, the life cycle of individuals and the regulation of population size.

The simulations follow the evolution of a population of individuals with discrete and non-overlapping generations. Individuals are characterized by L unlinked diploid loci, which additively determine the n-dimensional phenotype $\mathbf{z}$. According to the universal-pleiotropy assumption, each allele at each locus is specified by a vector of contributions to the n traits. We neglect environmental variance and, therefore, equate genotypic and phenotypic values. Mutations occur at rate u per (diploid) locus and have effects drawn from the distribution $p(\boldsymbol{\alpha})$ (eq. 4). Each generation, the following steps are performed:

(1) *Viability selection:* Individuals are removed with probability $1 - w(\mathbf{z})$ (eq. 1).

(2) *Population regulation:* If, after selection, the population size N exceeds the carrying capacity K, $N - K$ randomly chosen individuals are killed (Bürger 2000).

(3) *Reproduction:* The surviving individuals are randomly assigned to mating pairs, and each mating pair produces exactly B offspring (typically, $B = 4$). Note that, with this procedure, the effective size of a well-adapted population exceeds the

census size (e.g., for $B = 4$, $N_e = 4/3N$ p. 274 Bürger 2000). The offspring genotypes are derived from the parent genotypes by taking into account segregation, recombination and mutation.

To monitor adaptive substitutions, the program keeps track of the genealogical relationship between the alleles at a given locus. A substitution is recorded whenever there is a change in the root of such an "allele tree" (i.e., when the surviving alleles get a new most recent common ancestor). This is equivalent to calling an allele fixed if the entire population has been taken over by that allele or its descendants (e.g., Gillespie 1993; Park and Krug 2007).

In all simulations, the initial population contained $K = 1000$ identical, homozygous individuals with phenotype $\mathbf{0}$ (i.e., the population was perfectly adapted at time 0). The number of loci was set to $L = 10$ and the mutation rate per diploid locus to $\mu = 5 \cdot 10^{-6}$ per generation. This yields a population- and genome-wide mutation rate $\Theta = 2NLu = 0.2$. We chose this value to limit complications from interference between alleles co-segregating at the same locus, which have been thoroughly studied for the one-trait case in Kopp and Hermisson (2009b) (see Discussion). When comparing individual-based simulations to adaptive-walk simulations with differing Θ, the speed of environmental change $\mathbf{v}$ was adjusted accordingly to reach the same value of γ (eq. 13). Simulations were stopped after 1000 substitutions had been recorded. Alternatively, we only recorded the first adaptive substitution for 1000 replicate runs to study the initial phase of the adaptive process. Finally, for some parameter combinations, the simulations terminated because the population went extinct (e.g., if the environmental change was too fast).

3. Results

Our primary interest is the distribution of adaptive substitutions, that is, the distribution $\phi(\alpha)$ of the effects of those mutations that go to fixation and contribute to adaptation (eq. 12).

3.1. The distribution of adaptive substitutions and phenotypic complexity

Key properties of the distribution of adaptive substitutions can already be seen from a simplified model in which both mutation and selection are isotropic. Note that any model in which the two matrices $\mathbf{M}$ and $\mathbf{\Sigma}$ are proportional to each other, i.e., have the same shape and orientation, can be reduced to this case via the transformation described in

Supporting Information 2. The same holds true for any model under the environmentally-limited regime, in which the shape of the **M**-matrix is irrelevant (since any distribution of new mutations can be approximated by a uniform distribution).

In the isotropic model, the distribution of adaptive substitutions is symmetric around the direction of the moving optimum. Figure 1 shows this distribution in adaptive-walk simulations with $n = 2$ traits. The marginal distribution in the direction of the optimum has an intermediate mode and resembles a gamma distribution, in accordance with previous results for the one-dimensional moving-optimum model (Kopp and Hermisson 2009b), and in contrast to the exponential pattern predicted for the classical Fisher model with constant selection (Orr 1998). While the population always follows the optimum, pleiotropic side-effects of fixed mutations frequently lead to maladaptation of the traits under pure stabilizing selection. The distribution of these deviations is bell-shaped and centered around zero (Fig. 1).

For small γ, explicit analytical results can be obtained for the distribution of the first adaptive substitution in the environmentally-limited regime (Supporting Information 4, eq. S19). In particular, assuming $\mathbf{v} = (v_1, 0, \ldots, 0)$, the mean and variance in the direction of the optimum are given by

$$\mathrm{E}(\alpha_1|\mathbf{0}) = \bar{m}\left(\frac{\gamma}{\eta(n)(2\pi)^{-\frac{n}{2}}}\right)^{\frac{1}{n+3}} \Gamma\left(\frac{n+4}{n+3}\right) \tag{16}$$

$$\mathrm{Var}(\alpha_1|\mathbf{0}) = \bar{m}^2\left(\frac{\gamma}{\eta(n)(2\pi)^{-\frac{n}{2}}}\right)^{\frac{2}{n+3}} \left[\frac{n+5}{n+4}\Gamma\left(\frac{n+5}{n+3}\right) - \Gamma\left(\frac{n+4}{n+3}\right)^2\right], \tag{17}$$

where $\eta(n) = \frac{\pi^{\frac{n}{2}}}{(n+3)\Gamma\left(2+\frac{n}{2}\right)}$. Interestingly, the coefficient of variation $\sqrt{\mathrm{Var}(\tilde{\alpha}_1|\mathbf{0})}/\mathrm{E}(\tilde{\alpha}_1|\mathbf{0})$ depends only on n (see Fig. S4_2). The variance in directions orthogonal to the optimum is given by

$$\mathrm{Var}(\alpha_2|\mathbf{0}) = \frac{\bar{m}^2}{n+4}\left(\frac{\gamma}{\eta(n)(2\pi)^{-\frac{n}{2}}}\right)^{\frac{2}{n+3}} \Gamma\left(\frac{n+5}{n+3}\right). \tag{18}$$

Additional results regarding higher moments of α_1 and α_2, the total step size $\|\boldsymbol{\alpha}\|$ and the magnitude of pleiotropic deviations are given in Supporting Information 4.

In accordance with previous findings (Kopp and Hermisson 2007; Collins et al. 2007; Kopp and Hermisson 2009a,b), equations 16-18 show that the mean step size in the direction of the optimum increases with the scaled rate of environmental change γ, and

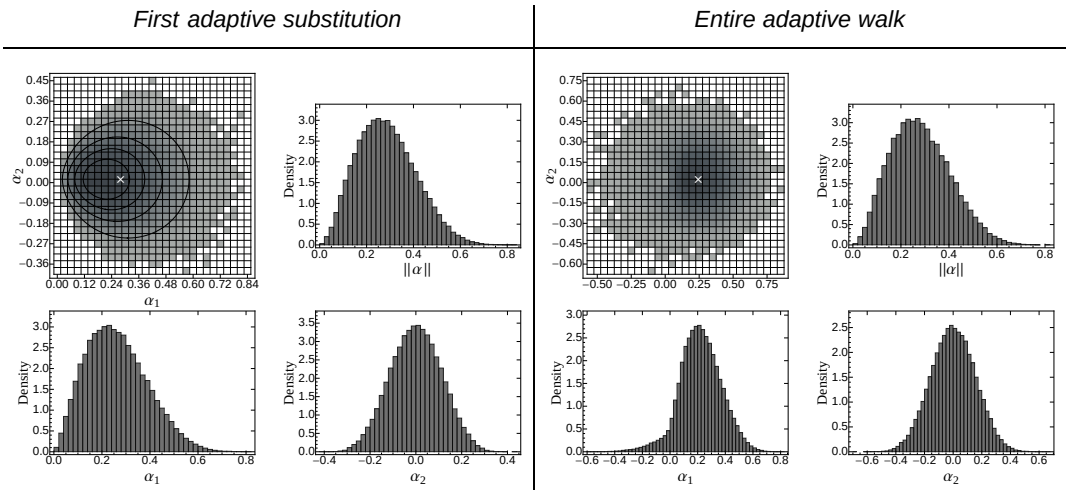

Figure 1 – The multivariate distribution of the first adaptive substitution (left) and for the entire adaptive walk (right) for $n = 2$ traits, when the optimum moves slowly in the direction of the first trait. In the top-left figures on each side, shades of grey indicate the frequency of a given step size in adaptive-walk simulations with normally-distributed mutational effects (with dark grey corresponding to high frequency), with the white cross showing the observed mean. The contour lines on the left represent the probability density predicted for a uniform distribution of new mutations (environmentally-limited regime, eq. S19; highest probability density intervals for $0.25, 0.5, 0.75, 0.95$ from inside out). Histograms show the marginal distribution of the first and second trait, α_1 and α_2, and the distribution of the total step size $||\boldsymbol{\alpha}||$. Parameter values are $v_1 = 10^{-5}, \Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0, m^2 = 1, \rho_M = 0$; the scaled rate of environmental change $\gamma = 10^{-4}$.

so does the magnitude of pleiotropic deviations (Fig. S4_1, S5_1). This fundamental relationship also holds true over the entire adaptive walk and beyond the environmental limit (Fig. 2, S5_2, S5_3).

Some discussion is warranted regarding the dependence of the mean step size on the average variance of mutational effects $\bar{m}^2$. Increasing $\bar{m}^2$ decreases γ and, consequently, leads to a reduced mean step size in the transformed phenotype space (see Supporting Information 2, eq. S28), where phenotypes are measured relative to $\bar{m}$. When phenotypes are measured in arbitrary units, however, the mean step size increases with $\bar{m}$ (eq. 16, see also Kopp and Hermisson 2009b). The reason is that an increase in $\bar{m}$ reduces the rate of appearance of small mutations (and, hence the parameter p_0 in the environmental limit, see eq. 15), which reduces the ability of the population to follow the optimum closely.

A key result of our analysis is that, for a given speed of environmental change, the mean step size in direction of the optimum increases with the number of traits under selection, that is, with the level of pleiotropy or organismic complexity (eq. 16, Fig. 2, S4_1, see also Fig. S5_2 and S5_3), and a similar result also holds for fitness (Fig. S5_4). At first, this result seems to contradict the "cost of complexity" argument from Fisher's model,

which states that, in complex organisms, large mutations are unlikely to contribute to adaptation. The explanation is that, precisely because fewer mutations are beneficial if n is large (because there are more directions in which they can "go wrong"; Orr 1998), the time to the first step increases (see Supporting Information 4). By this time, the optimum has already moved considerably, such that also large mutations are beneficial (see Supporting Information 1 and Fig. S1_1), even if they have significant pleiotropic effects. These effects – in particular, the increased waiting time between adaptive substitutions – also affect population persistence: as shown in Figure S5_5, the mean time to extinction decreases with organismic complexity, and so does the maximal rate of environmental change a population can tolerate (Bürger and Lynch 1995).

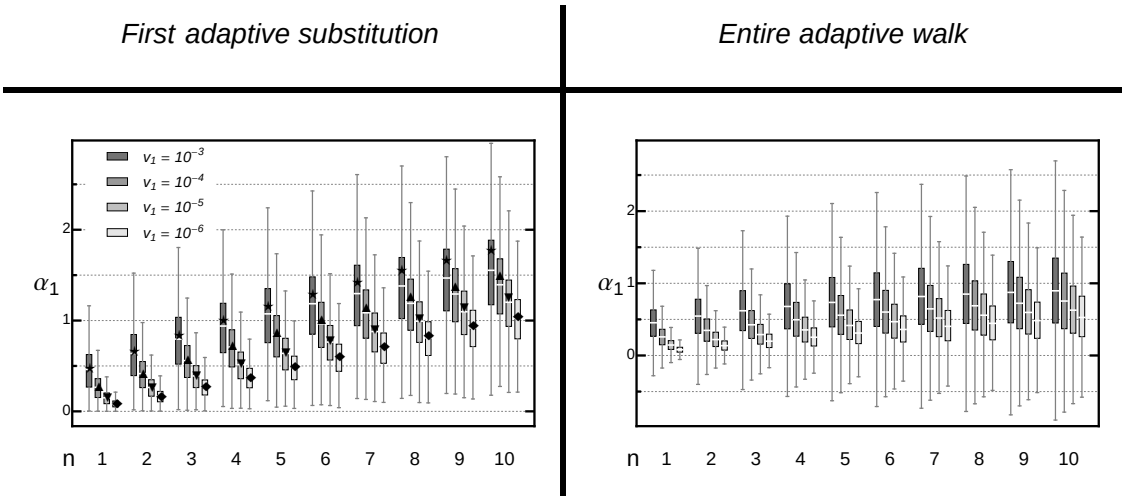

Figure 2 – Distribution of the size α_1 of the first adaptive substitution (left) and for the entire adaptive walk (right) in the direction of the moving optimum, as a function of phenotypic complexity n for different rates of environmental change v_1. Symbols in the left-hand panel show the predicted mean of the first adaptive substitution when assuming a uniform distribution of mutational effects (environmentally-limited regime, eq. 16). This approximation produces a good match as long as the predicted $\bar{\alpha}_1$ does not exceed the (mean) standard deviation of the effects of new mutations ($\bar{m} = 1$). Beyond this mark, the realized step size is reduced due to limited availability of large-effect mutations. Compared to the first-step, the increase of $\bar{\alpha}_1$ with n is less pronounced when considering the entire adaptive-walk. The reason is that subsequent substitutions will often compensate for pleiotropic side effects of previous steps rather than follow the moving optimum. Boxplots are based on 10000 replicated adaptive-walk simulations. The box contains 50% of the data. Horizontal white bars indicate the mean step size $\bar{\alpha}_1$. Whiskers extend to maximally 1.5 times the size of the box. Outliers are not shown. Parameters: $\sigma^2 = 10, \rho_\Sigma = 0, \Theta = 1, m^2 = 1, \rho_M = 0$; the scaled rate of environmental parameter $\gamma = 10 \cdot v_1$.

3.2. Selectional and mutational correlations

To study the orientation of the distribution of step sizes in the n-dimensional phenotype space, we now consider a model with correlated selection and correlated mutations. We will assume that the angle between the direction of the optimum $\mathbf{v}$ and the leading eigenvector of $\boldsymbol{\Sigma}$ and/or $\mathbf{M}$ is 45°. More precisely, the optimum moves along the first trait axis

($\mathbf{v} = (v_1, 0, \ldots)'$), whereas the fitness landscape and/or the distribution of new mutations are concentrated along the main diagonal: All diagonal elements of $\mathbf{\Sigma}$ ($\mathbf{M}$) are equal to σ^2 (m^2) and all off-diagonal elements have magnitude $\rho_\Sigma\sigma^2$ ($\rho_M m^2$), where $1 > \rho_\Sigma \geq 0$ ($1 > \rho_M \geq 0$) is the magnitude of selectional (mutational) correlation. In this case, the fitness landscape (distribution of new mutations) is symmetric around the leading eigenvector of $\mathbf{\Sigma}(\mathbf{M})$, $\boldsymbol{\nu} = (1, 1, 1, \ldots)$. We first study the effects of mutational and selectional correlation separately. Exemplary adaptive walks for strong correlations are shown in Figure 3.

Figure 4 shows the multivariate distribution of adaptive substitutions, $\phi(\boldsymbol{\alpha})$, for different strengths of selectional and mutational correlations under varying speeds of environmental change for $n = 2$ traits. As in the isotropic case (Fig. 1), the distribution $\phi(\boldsymbol{\alpha})$ is biased towards the direction of the optimum, with pleiotropic side-effects of fixed mutations on average being neutral (Fig. S5_6, S5_7). The shape of the distribution, however, critically depends on the interaction between the type and strength of correlations and the rate of environmental change. Mutational correlations tend to align the distribution of adaptive substitutions along the leading eigenvector of $\mathbf{M}$, with stronger mutational correlations leading to stronger correlation in step sizes (Fig. 4, Fig. 5 and S5_8 top left). This effect is strongest in fast-changing environments and gradually gets weaker as the rate of environmental change decreases (Fig. 5), until becoming almost unnoticeable. Selectional correlations similarly orientate the distribution of adaptive substitutions along to the leading eigenvector of $\mathbf{\Sigma}$ (Fig. 4, 5 bottom left, S5_8). In contrast to mutational correlations, however, their impact is strongest if environmental change is slow (for small γ and the first step, the correlation is given by $\rho_\Sigma \sqrt{\frac{\mathrm{Var}(\alpha_2|\mathbf{0})}{\mathrm{Var}(\alpha_1|\mathbf{0})}} \approx \rho_\Sigma$, see eq. S36). Correlations in step sizes remain almost unchanged for a broad range of rates v_1, before dropping off sharply once environmental change gets sufficiently fast.

These results still hold true when mutational and selectional correlations are both present but with opposite signs. As shown in Figure 6, the correlations in step sizes resemble the selectional correlations if environmental change is slow and resemble the mutational correlations if environmental change is fast. At intermediate rates of environmental change, the two effects cancel, and correlations in step sizes are close to zero.

Mutational and selectional correlations depend on the coordinate system in which multivariate phenotypes are measured (i.e., on the definition of traits). As shown in Supporting Information 2, there is always a transformation to coordinates in which selection (but not necessarily mutation) is isotropic. The key question, therefore, is whether or not the distribution of new mutations is aligned with the fitness landscape (in terms of the

eigensystems/principle components of the matrices $\mathbf{M}$ and $\mathbf{\Sigma}$). Our results can, thus, be reformulated as follows: The distribution of adaptive substitutions reflects the shape and orientation of the fitness landscape if adaptation is environmentally limited (i.e., if the optimum changes slowly), whereas it mirrors the distribution of new mutations (but with a mean shifted in the direction of the optimum) if adaptation is genetically limited (i.e., if the environment changes fast). Intuitively, as long as environmental change is slow, the population is close to the optimum and the shape of the distribution of new mutations is practically irrelevant, because only a small subset of new mutations from the center of their distribution can pass the selective sieve (Kopp and Hermisson 2009b). In contrast, if environmental change is fast, the population is far from the optimum, and the selective sieve has less impact on the adaptive process than the supply with new mutations. In the limit, pleiotropic side effects become negligible and the selection coefficient of new mutations depends only on their effect in the direction of the optimum.

Finally, mutational and selectional correlations also impact the trajectory of the mean phenotype (Fig. 3, 5, S5_8; see also Jones et al. 2004). In particular, strong mutational correlations can cause the mean phenotype to trail above and behind the moving optimum – an effect that has been phrased the "flying-kite effect" (Jones et al. 2004). Conversely, with strong (positive) selectional correlation, the phenotypic mean follows the optimum behind and below. In analogy to the flying-kite effect, we call this phenomenon the "diving-kite effect". Both effects can be explained by a deterministic model in which the change in the mean phenotype depends primarily on the leading eigenvector of $\mathbf{M}$ and the selection gradient $\boldsymbol{\beta}(t)$ (Figure 7). Under strong mutational correlation, the change in mean phenotype is initially dominated by the leading eigenvector of $\mathbf{M}$, causing the "rise of the kite", until it is balanced by the selection gradient pointing towards the optimum. Under strong selectional correlation, however, the selection gradient is initially orthogonal to the leading eigenvector of $\mathbf{\Sigma}$ (i.e., the "ridge" of the fitness landscape), causing the mean phenotype to "dive". Again, the trajectory will gradually change until it is aligned with the direction of the moving optimum (where it is aligned with the axis of largest width of the fitness landscape). Observing either the flying or the diving kite requires a sufficiently fast-changing environment (the kite needs to be pulled strongly enough) and at least intermediate levels of mutational or selectional correlations (right column Fig. 5, S5_8). As the number of traits increases, the strength of both effects decreases on a per-trait basis, but their total strength increases (Supporting Information 4 and Fig. S4_1). Independently of the number of traits, the population on average takes smaller steps in the direction of the optimum as correlations (either selectional or mutational) become stronger (Fig. S5_2, S5_3).

3.3. Accuracy of the approximations

Our main analytical tool has been the adaptive-walk approximation with normally distributed mutational effects. When compared to individual-based simulations of an explicit genetic model, its performance is often surprisingly good (e.g., Fig. 4, 5, S5_2, S5_3, S5_8). Significant deviations occur mainly if the population-wide mutation rate Θ is high ($\Theta \gg 1$), which, in violation of the adaptive-walk assumption, increases the probability of co-segregating beneficial mutations (Discussion and Fig. S5_9, S5_10). Since the adaptive-walk approximation does not account for population dynamics, it cannot be used to predict population persistence or extinction. Individual-based simulations show that long-term persistence is often impossible if the scaled rate of environmental change γ exceeds 0.1 (corresponding to $v_1 = 0.01$ in Fig. 6, S5_2, S5_3).

For slow environmental change, the normal distribution of new mutations can, furthermore, be approximated by an appropriate uniform distribution. The resulting approximation for adaptive walks works well for a broad range of small to intermediate rates of environmental change (see insets in Fig. S5_2). Naturally, this approximation cannot capture mutational correlations (see the poor fit for high values of ρ_M and v_1 in Fig. S5_3). Note, however, that for sufficiently small rates of environmental change, mutational correlations can, indeed, be ignored (see above, Fig. 4, 5).

Finally, we have attempted to approximate the distribution of adaptive substitutions over an entire adaptive walk by the distribution of the first step. This approximation works well in the one-trait case (Kopp and Hermisson 2009b), and in combination with a uniform distribution of new mutations, it is the only approach that allowed significant analytical progress (Supporting Information 4). With multiple traits, however, the first step makes a larger progress towards the optimum than the subsequent steps (Fig. 2,S5_2, S5_3). The reason is that the first step will always introduce maladaptive pleiotropic side-effects, which become compensated for by subsequent substitutions. Some of these compensatory substitutions are "backward steps", which are beneficial, despite their effect being opposite to the direction of the optimum (e.g. Supporting Information 1, grey ellipse in Figure S1_1 and "backward-steps" in Figure 1 and 4). Consequently, the first-step approximation works less well as the number of traits increases (Fig. S5_1). Furthermore, with mutational or selectional correlations, the direction of the first step systematically deviates from the distribution of step sizes over the entire adaptive walk (see flying and diving-kite effects above; for the case of selectional correlation, see Fig. S5_11).

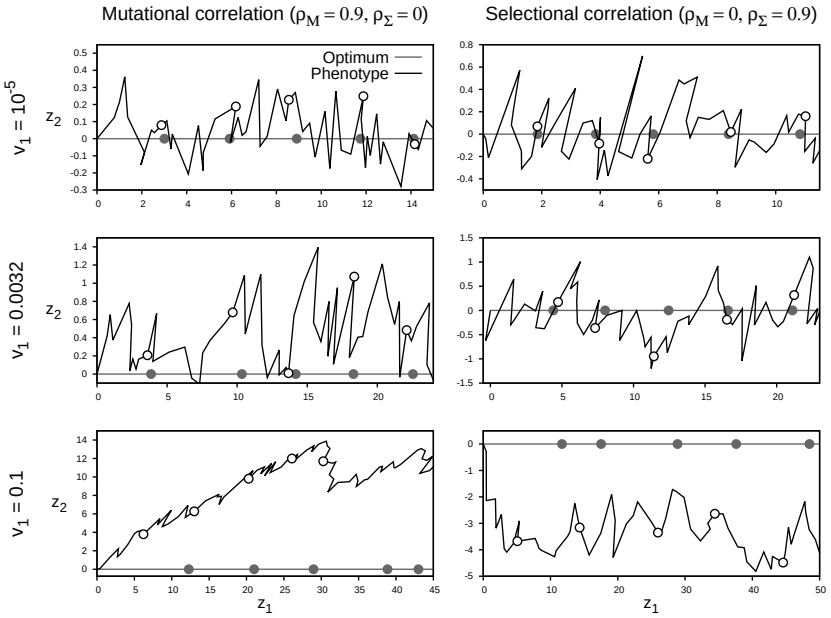

Figure 3 – Example trajectories of the mean phenotype $\bar{\mathbf{z}} = (\bar{z}_1, \bar{z}_2)$ from adaptive-walk simulations with $n = 2$ traits and strong mutational or selectional correlation, for three different rates of environmental change v_1 (Fig. 4). Open circles mark the state of the population after $10, 20, 30, 40$ and 50 adaptive substitutions. Closed circles give the corresponding positions of the moving optimum. The bottom row illustrates the flying- and diving-kite effect, respectively. Other parameters: $\Theta = 1, \sigma^2 = 10, m^2 = 1$.

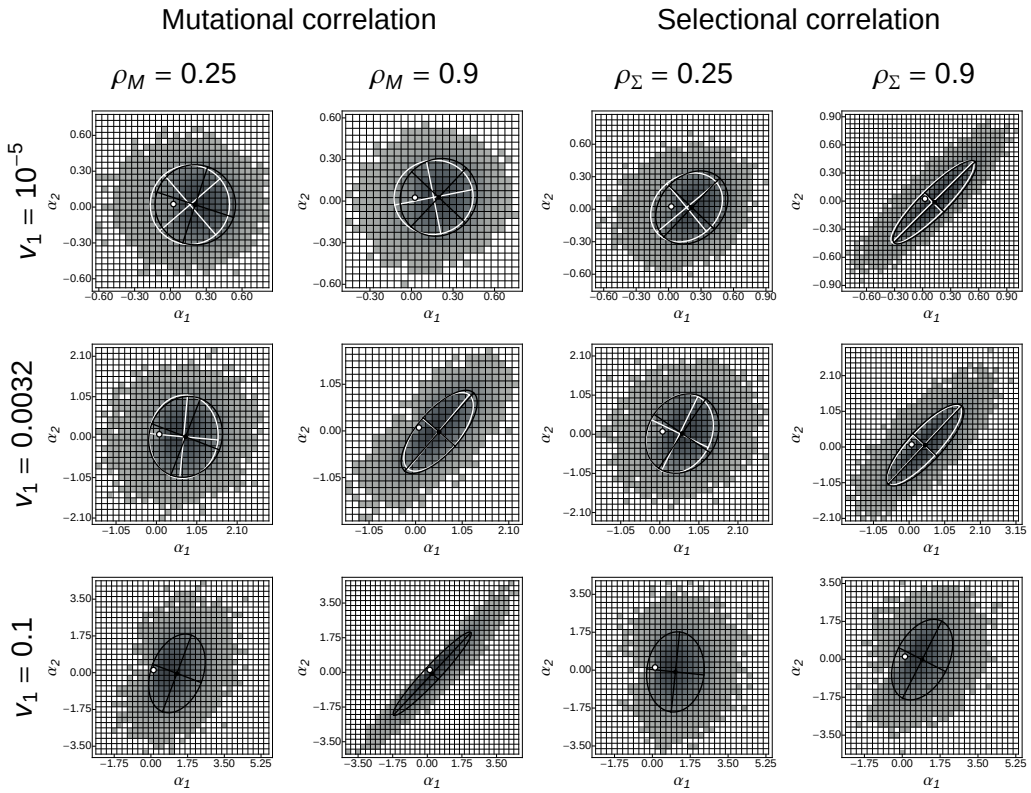

Figure 4 – The distribution of adaptive substitutions for $n = 2$ traits under mutational or selectional correlation and their dependence on the speed of environmental change v_1. Shades of grey indicate the frequency of a given step size in adaptive-walk simulations, and dark ellipses are the corresponding 90%-confidence ellipses (based on the empirical covariance matrix). Light ellipses are 90%-confidence ellipses for the step-size distribution from individual-based simulations (absent for $v_1 = 0.1$ because simulated populations went extinct). The white dots mark the origins of the coordinate systems. Columns 1 and 2 are for weak and strong mutational correlations, respectively, with uncorrelated selection ($\rho_\Sigma = 0$). Columns 3 and 4 show results for selectional but no mutational correlation ($\rho_M = 0$). Remaining parameters: $\Theta = 1, \sigma^2 = 10, m^2 = 1$.

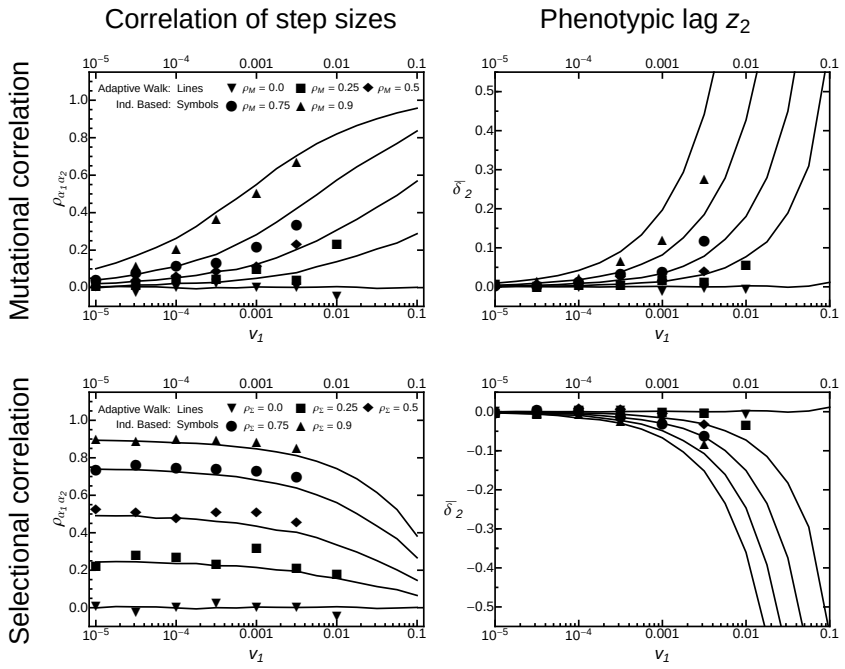

Figure 5 – The impact of mutational and selectional correlations on the distribution of adaptive substitutions for $n = 2$ traits. The left-hand column shows the correlation ρ_{α_1,α_2} between step sizes in the direction of the moving optimum (α_1) and in an orthogonal direction (α_2), for different values of mutational (top row) and selectional (bottom row) correlation ρ_Σ and ρ_M, plotted as a function of the rate of environmental change v_1. The right-hand column shows δ_2, that is, the phenotypic lag in the direction orthogonal to the moving optimum, demonstrating the flying- and diving-kite effects (top and bottom, respectively). Lines show results from adaptive-walk simulations, whereas symbols are from individual-based simulations. Remaining parameters: $\Theta = 1, \sigma^2 = 10, m^2 = 1$.

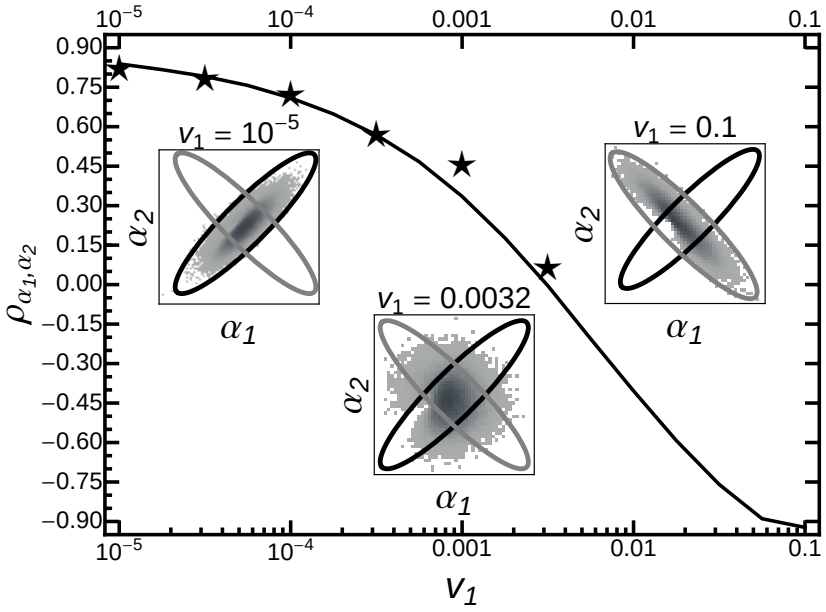

Figure 6 – Correlation between steps in direction of the moving optimum and in an direction orthogonal to the moving optimum, ρ_{α_1,α_2}, as function of the rate of environmental change v_1, for strong and antagonistic mutational and selection correlation. The black line shows results from adaptive-walk simulations, while the stars give the corresponding individual-based simulation results. Insets give the distribution of adaptive substitutions retrieved from the adaptive-walk simulations for $v_1 = 10^{-5}, v_1 = 0.0032$ and $v_1 = 0.1$, with shades of grey indicating the frequency of a specific step size (dark grey indicating high frequency). The black and gray ellipses show the shape of the fitness landscape and the shape of the distribution of new mutations, respectively. Note that individual-based simulations died out for $v_1 > 0.0032$. Remaining parameters: $\Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0.9, m^2 = 1, \rho_M = -0.9$.

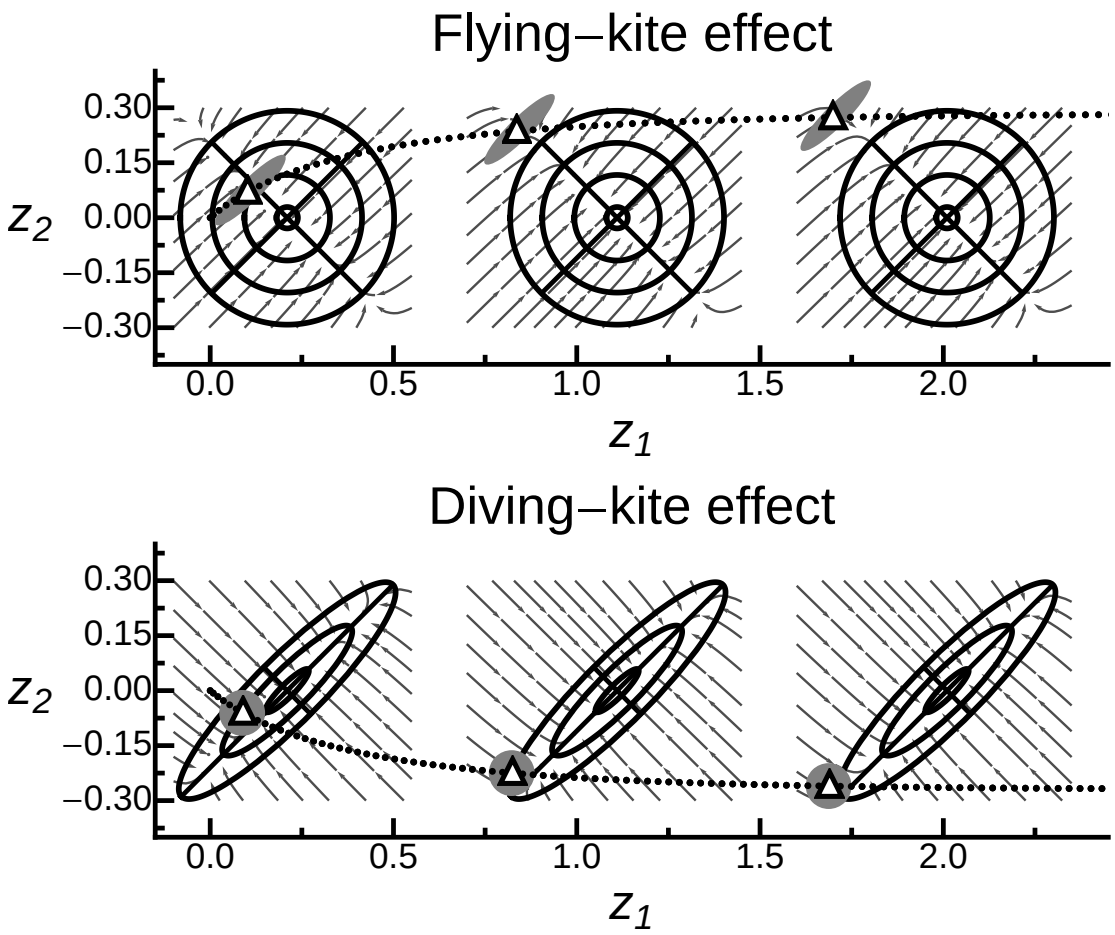

Figure 7 – Schematic illustration of the flying- (top) and diving-kite effects (bottom) in a deterministic approximation, with snapshots taken at the initial (left), intermediate (middle) and equilibrium (right) phases. For each snapshot, the black ellipse represents the fitness landscape (defined by the **Σ**-matrix), the grey ellipse gives the shape of the distribution of new mutations (the **M**-matrix), the white triangle gives the current position of the mean phenotype, and dots show its trajectory. Grey arrows represent hypothetical trajectories towards a constant optimum if the population were placed at the beginning of the arrow. Results are based on the "canonical equation" of adaptive dynamics (Dieckmann and Law 1996), which states that the mean phenotype $\bar{\mathbf{z}}$ changes according to $\Delta\bar{\mathbf{z}} = \mathbf{M}\boldsymbol{\beta}(t)$, where $\boldsymbol{\beta}(t) = (\boldsymbol{\Sigma} + \mathbf{M})^{-1}\left(\mathbf{z}_{\text{opt}}(t) - \bar{\mathbf{z}}(t)\right)$ (Jones et al. 2004) is the selection gradient (which points in the direction of steepest ascent on the fitness landscape). (Note that the canonical equation is structurally identical to the Lande equation from quantitative genetics (Lande 1979, 1980; Jones et al. 2004) if the **M**-matrix is replaced by the **G**-matrix of standing genetic variation.) Without selectional correlation (top row), the selection gradient always points towards the current optimum. Without mutational correlation (bottom row), the selection gradient is parallel to the grey arrows.

4. Discussion

Environmental change forces populations to either adapt to the altered conditions or go extinct. In the absence of standing genetic variance for fitness, the outcome crucially depends on mutations, which provide the "genetic fuel" for adaptation, and selection which converts this resource into adaptive substitutions. Here, we have used analytical approximations and individual-based simulations to study the effects of pleiotropy or "organismic complexity" on the genetic basis of adaptation in gradually changing environments. In particular, we have investigated the distribution of adaptive substitutions (i.e., the distribution of the phenotypic effect sizes of fixed mutations) in populations following a moving optimum. Our results confirm and extend previous analysis of "adaptive walks" for single traits (Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b). We show that the distribution of adaptive substitutions is largely determined by a single composite parameter γ, which scales the rate of environmental change relative to the "adaptive potential" of the population and defines a continuum between environmentally- and genetically-limited adaptation (Kopp and Hermisson 2009b). In the environmentally-limited regime (slow environmental change), the population follows the optimum closely, adaptive steps are small and their multivariate distribution mirrors the shape of the fitness landscape. In the genetically-limited regime, in contrast, the population follows the optimum with a large gap, adaptive steps are large and their distribution is determined primarily by the distribution of new mutations. We furthermore show that the mean effect size of fixed mutations increases with the degree of pleiotropy, in contrast to classical predictions from Fisher's geometric model (FGM) under sudden environmental change. We now discuss these results in greater detail.

4.1. The effect of phenotypic complexity on the genetics of adaptation

In complex organisms, pleiotropy is wide-spread, that is most mutations affect multiple traits simultaneously. Different traits, therefore, do not evolve independently (Lande 1979; Walsh and Blows 2009; Agrawal and Stinchcombe 2009). With this basic fact in mind, Fisher (1930) used his classical geometric model to argue for a predominance of small mutations in adaptive evolution. While theoretical studies later pointed out that large beneficial mutations may, nevertheless, play an important role (Kimura 1983; Gillespie 1993; Orr 1998, 2005a), they also confirmed that organisms pay a "cost of complexity" (Orr 1998, 2000; Welch and Waxman 2003) in the form of a reduced rate of adaptation. With regard to individual substitutions, Orr (2000) found that more complex organisms make smaller steps when adapting towards a fixed optimum (with step size

measured as the decrease in the absolute distance to the optimum, which is closely related to the fitness effect of a fixed mutation). This is in direct contrast to our results for a moving optimum, where increased complexity leads to larger step sizes, with respect to both phenotype and fitness (Fig. 2, S5_4).

The main reason for this finding arises from the ecological differences between the classical FGM and the moving optimum model (consequences of different mutation models are discussed below). In the classical Fisher model, the proportion of beneficial mutations decreases with organismic complexity. Thus, the more phenotypic traits, the longer one has to wait for a beneficial mutation to appear (as adding another trait adds yet another dimension where mutations can go wrong; eq. S18). Of course, this argument still holds true under a moving optimum. As more complex organisms have to wait longer for a beneficial mutation to appear, the optimum has already travelled farther, enabling larger mutations to become fixed. Thus, the moving-optimum model does not contradict the "cost of complexity" argument, but reveals yet another aspect of it.

4.2. Adaptation under mutational and selectional correlations

The impact of mutational and selectional correlations on the distribution of adaptive substitutions is a direct consequence of the general principle that the shape of this distribution depends on the scaled rate of environmental change (see above). In particular, if the rate of environmental change is slow, only mutations from the very center of the mutational distribution can pass the selective sieve (Kopp and Hermisson 2009b), making mutational correlations irrelevant relative to the shape of the fitness landscape. Conversely, if adaptation is genetically-limited, the selective sieve has less impact on the adaptive process than the supply with new mutations. Between these two extremes, the distribution of adaptive substitutions will progressively take the orientation of the mutational distribution as the rate of environmental change increases (Fig. 6).

Our results reveal strong parallels between the distribution of adaptive substitutions and the evolution of the **G**-matrix describing standing genetic variation (see also below). Recent quantitative-genetic studies have shown that both mutational and selectional correlations can induce correlations in the **G**-matrix, under both constant stabilizing and moving-optimum selection (Jones et al. 2003, 2004). A link between selectional correlation and genetic correlation has also been confirmed empirically (see Roff and Fairbairn (2012) for a recent meta-analysis). As shown in Figure S5_13, the distribution of adaptive substitutions closely matches the shape and orientation of the **G**-matrix. While this seems intuitive, it had not been shown by any previous study, and little is known about

the relation between alleles in the standing variation and those that ultimately reach fixation (but see Hill 1982; Hill and Rasbash 1986a,b). This close correspondence between standing variation and fixed mutations might explain why the adaptive-walk approximation works surprisingly well even in populations with a high mutation rate (see Kopp and Hermisson 2009b). Quantitative-genetic studies have, so far, not systematically investigated how correlations in the **G**-matrix are affected by the rate of environmental change. It would be interesting to know whether the effects of mutational and selectional correlations on the **G**-matrix are similar to those on the distribution of adaptive substitutions.

Confirming previous results by Jones et al. (2004), our simulations showed that mutational and selectional correlations can cause systematic maladaption in traits under purely stabilizing selection (i.e., in directions orthogonal to the direction of the optimum). These "flying-" and "diving-kite" effects require that correlations are strong and the environmental change is sufficiently fast (i.e., in the genetically-limited regime, see Fig. 3 and 5). Strong effects are, therefore, likely to be restricted to a narrow parameter range, where populations might often be on the brink of extinction.

4.3. Discussion of the model assumptions and future directions

Like all models, our study is based on a number of simplifying assumptions, which might constrain the generality of our results. In the following, we discuss the likely consequences of these assumptions, potential extensions of the model, and ways to test our predictions empirically.

First, our model is based on the assumption of universal pleiotropy (Kacser and Burns 1981; for a review see Paaby and Rockman 2013). This assumption has been challenged recently, both because empirical levels of pleiotropy are rather low (median 1-7; Wang et al. 2010) and because true universal pleiotropy would induce unsustainably high costs ("the cost of complexity [...] should be more properly called the cost of pleiotropy" Wagner and Zhang 2012, but see Hill and Zhang 2012a). Alternative approaches have, therefore, suggested modularity (Wagner and Altenberg 1996; Welch and Waxman 2003) or partial pleiotropy (Chevin et al. 2010; Lourenco et al. 2011) as a solution to this problem. Indeed, our model might be best interpreted as applying to a given module with a moderate level of pleiotropy. In any case, the relatively low number of traits assumed in most parts of this paper is consistent with the degree of pleiotropy observed in natural populations (Martin and Lenormand 2006a,b; Wang et al. 2010). Thus, we expect our results to apply across a wide range of species facing environmental change.

Second, we assume the so-called Euclidean-superposition model (Turelli 1985; Wagner 1988), where the distribution of mutational effects on a given trait is independent of complexity (see also Welch and Waxman 2003; Lourenco et al. 2011; Zhang 2012). Other studies (Orr 1998, 2000; Wingreen et al. 2003; and an alternative model in Welch and Waxman 2003) have instead used a "constant total-effects model", in which the total mutational effect size ($||\boldsymbol{\alpha}||$) is constant across levels of complexity and, in consequence, the mean effect size on individual traits decreases. Indeed, this assumption explains part of our differences to Orr (1998, 2000). More generally, it raises the question of which factor is more important in shaping the distribution of adaptive substitutions at different levels of complexity: the "pleiotropic scaling" of mutations (Wagner et al. 2008) or the mode of environmental change. To address this issue, we conducted additional simulations, which combined constant and moving-optimum selection with the Euclidean-superposition and constant-total-effect models. These simulations yielded three main results (Fig. S5_12). First, the moving-optimum model behaves qualitatively similarly under both mutation models; in particular, average step size increases with complexity (at least as long as adaptation remains environmentally limited). This shows that our main results are robust to considerable variation in the pleiotropic scaling of mutational effects. Second, with a constant optimum, the mutation model does make a qualitative difference for the mean step size in the direction of the optimum (but not for total step size $||\boldsymbol{\alpha}||$), which decreases with complexity under the constant-total effects model, but increases under the Euclidean-superposition model. Third, a fundamental difference between constant and moving-optimum selection, which is independent of the mutation model, is seen at the level of the selection coefficients of fixed mutations, which decrease with complexity under a constant optimum but increase with complexity under a moving optimum. In summary, the mode of environmental change plays a fundamental role in shaping the distribution of adaptive substitutions and, in many cases, overrides the effects of pleiotropic scaling. Nevertheless, a better understanding of pleiotropic scaling – both empirically (Wagner et al. 2008; Hermisson and McGregor 2008; Wang et al. 2010; Wagner and Zhang 2011; Hill and Zhang 2012b) and with respects to its theoretical consequences – clearly is an important topic for future research.

Third, our adaptive-walk approximation assumes that evolution proceeds as a series of (hard) selective sweeps originating from new mutations. This follows the tradition of models based on a strong-selection-weak-mutation approximation (Gillespie 1983; Orr 1998, 2005a). In contrast, quantitative-genetic models assume that virtually all adaptation stems from standing genetic variation (in the context of the moving-optimum model, see e.g. Bürger and Lynch 1995; Gomulkiewicz and Holt 1995; Jones et al. 2004, 2012;

Zhang 2012; Chevin 2013; see also Fig. S5_13), and the importance of standing variation is well documented empirically (Hermisson and Pennings 2005; Barrett and Schluter 2008; Gomulkiewicz and Houle 2009; Teotónio et al. 2009; Jerome et al. 2011; Domingues et al. 2012; Messer and Petrov 2013). So far, quantitative-genetic models with a multidimensional moving optimum have focused either on the risk of population extinction (Gomulkiewicz and Houle 2009) or the maintenance and structure of genetic variation (Jones et al. 2004, 2012). To our knowledge, very little is known about the distribution of phenotypic effect sizes of adaptive substitutions when adaptation occurs from standing genetic variation. Since in this case the adaptive process is likely to have very different properties (e.g., adaptation could be faster with on average smaller mutations becoming fixed Barrett and Schluter 2008; Rockman 2012), this should be an important topic for future research.

Fourth, in accordance with the adaptive-walk approximation, most of our simulations (including those in Fig. 6) assumed a relatively (but not unrealistically) low population-wide mutation rate Θ. As such, we ignore effects of interactions between co-segregating beneficial mutations. For the one-dimensional case, Kopp and Hermisson (2009b) showed that high mutation rates in combination with low recombination (or a small number of loci) lead to an increase in the mean size of adaptive substitutions, due to Hill-Robertson interference (Hill and Robertson 1966; Gerrish and Lenski 1998). At high recombination rates (or with a large number of unlinked loci), in contrast, the mean step size decreases as a result of epistasis for fitness (due to stabilizing selection). Individual-based simulations suggest that these results also hold true for the multivariate case (Fig. S5_9, S5_10). Note, however, that the strength of interference is expected to decrease with increasing complexity, since the rate of beneficial mutations decreases.

In addition, Hill-Robertson interference also influences how the distribution of adaptive substitutions is affected by mutational and selection correlations. In particular, correlations between adaptive substitutions increase with increased linkage in the presence of mutational correlations (Fig. S5_9), but decrease with linkage in the presence of selectional correlations (Fig. S5_10). Thus, at high mutation rates, increasing linkage has a similar effect as increasing the scaled rate of environmental change γ. This makes intuitive sense, since interference weakens the efficiency of selection (Gerrish and Lenski 1998; Weissman and Barton 2012), which brings the adaptive process closer to the genetically-limited regime.

Finally, our adaptive-walk approximation does not consider population dynamics. By setting an arbitrary extinction-threshold with respect to mean fitness, we found that the maximal rate of environmental change a population can tolerate (Bürger and Lynch

1995), as well as the mean time to extinction, decreases with the number of traits (Fig. S5_5; this result is also supported by individual-based simulations). In particular, in complex organisms, long-term persistence in the face of an indefinitely moving optimum seems to be possible only in the environmentally-limited regime ($\gamma \lesssim 0.1$), that is, when adaptation is not limited by the availability of new mutations. In the genetically-limited regime, in contrast, populations can only persist for a limited amount of time (e.g., fast environmental change followed by a period of stasis). Over shorter timescales and with high mutation rates (large Θ, as in Jones et al. 2004), population persistence can also be facilitated by adaptation from standing genetic variation (Bürger and Lynch 1995; Barrett and Schluter 2008; Gomulkiewicz and Houle 2009). Indeed, our parameter γ is structurally similar to expressions describing the equilibrium phenotypic lag in quantitative genetic models of adaptation to a moving optimum (eq. 5 in Jones et al. 2004; see also eq. 8a in Bürger and Lynch 1995). The interpretation is analogous: the lag increases with the speed of environmental change, and decreases with the strength of selection and the amount of (standing) genetic variation.

Our model makes a number of concrete predictions (Tab. 1) that can be tested empirically, even though such tests will certainly be challenging. The most direct approach is experimental evolution (for reviews see Elena and Lenski 2003; Kawecki et al. 2012; Barrick and Lenski 2013). While the majority of studies have employed constant conditions (Reusch and Boyd 2013), Collins (2011b) recently urged for more studies in gradually changing environments. Microorganisms such as bacteria, yeast or algae can be cultivated in media where an environmental factor such as temperature (Hietpas et al. 2013), salinity (Bell and Gonzalez 2009; Lachapelle and Bell 2012), pH (Hughes et al. 2007), the availability of nutrients (Collins 2011a), or the concentration of stressors such as antibiotics (Perron et al. 2008; Lindsey et al. 2013) or pollutants (Adamo et al. 2012) is gradually changed. Until now, these studies were mainly used to investigate the probability of "evolutionary rescue" (Gonzalez et al. 2013). Recent advances in sequencing technologies (reviewed in Metzker 2010), however, make it possible to conduct real-time genome-wide analyses and to map genetic changes to their effects on phenotype and fitness (Barrick et al. 2009; Barrick and Lenski 2013), such that the distribution of adaptive substitution over entire adaptive walks can be analyzed.

In natural populations, where only present-day data are available, the most promising approach for studying the genetic basis of adaptation is the analysis of quantitative-trait loci (QTLs) in diverging populations. For example, Langlade et al. (2005) identified QTLs for leaf shape in two species of *Antirrhinum* and postulated a sequence of substitutions that can traverse the "allometric space" between them. Albert et al. (2008) and

Rogers et al. (2012) analyzed genetic differences between ancestral marine and derived freshwater populations of sticklebacks (*Gasterosteus aculeatus*). Rogers et al. (2012) compared two sets of freshwater populations and showed that those whose environment (and presumably phenotypic optimum) is more different from that of the marine populations (with respect to salinity and presence of predators) displayed a higher frequency of large-effect QTLs. Albert et al. (2008) crossed an ancestral Pacific and a highly derived benthic freshwater form and found a gamma-like distribution of QTL effect sizes with an intermediate mode. Taking into account the detection limits for small-effect QTLs (Otto and Jones 2000), they interpreted this result as support for Fisher's geometric model with constant selection (i.e., the difficulty in identifying small QTLs would turn the predicted exponential distribution into an observed gamma-like distribution). However, both studies could, in principle, also be interpreted as showing the outcome of adaptation to a moving optimum (as briefly discussed in Schluter et al. 2010; Rogers et al. 2012), which directly predicts a distribution of effect sizes with an intermediate mode. More stringent tests of the present theory would require studying populations for which a moving optimum can be assumed *a priori* (e.g., comparisons of microalgae from pristine habitats with populations known to have experienced gradual eutrophication). Even then, the difficulty in detecting small-effect substitutions will remain a major challenge (Otto and Jones 2000).

4.4. Conclusion

Natural populations are constantly forced to adapt to changing environments, a process that takes place in a high-dimensional phenotype and genotype space. Along with previous studies, our analysis of the moving-optimum model shows that the genetic basis of this process depends critically on the tempo and mode of environmental change. In particular, our environmentally- and genetically-limited regimes lead to qualitative differences in the distribution of adaptive substitution, with respect to its mean, shape and correlation patterns. Long-term persistence is likely restricted to the environmentally-limited regime – where adaptation proceeds "smoothly" in small steps – but the parameter range for this regime is reduced in complex organisms.

Acknowledgements

We thank Reinhard Bürger, associate editor Ophélie Ronce and two anonymous reviewers for constructive comments on this manuscript. This study was supported by Austrian

Science Fund, FWF (grant P 22581-B17) to MK, Austrian Agency for International Cooperation in Education and Research, OEAD (grant FR06/2014) to JH, and a Writing-Up Fellowship from the Konrad Lorenz Institute for Evolution and Cognition Research to SM.

Table 1 – A summary of theoretical predictions of the moving-optimum model.

How does ... affect adaptation?	**Theoretical prediction**
Mode of environmental change	
Sudden change	The distribution of adaptive substitution is approximately exponential with respect to phenotype and fitness. Accordingly, most fixed mutations are of small effect and only a few large-effect alleles become fixed when approaching the constant optimum. The farther the optimum is away (i.e., the harsher the sudden environmental change) the larger the mutational effects that get fixed.
Gradual change	The distribution of adaptive substitution with respect to phenotype (in the direction of the optimum or total effect) and fitness is gamma-like with an intermediate mode (Fig. 1, S5_4). Thus, when following the moving-optimum, most adaptive substitutions are of intermediate effect with only a few large-effect alleles becoming fixed.
Scaled rate of environmental change	
	The faster the rate of environmental change relative to the adaptive potential, the larger the mutational effects that become fixed. Holds true with respect to phenotype and fitness (Fig. 2, S5_4). With increasing rate of environmental change the distribution of fitness effects becomes more asymmetric.
Complexity/Pleiotropy	
	Mean effect of adaptive substitutions with respect to phenotype and fitness increases as the number of traits affected by a single mutation increases (Fig. 2, S5_12).
Mutational correlation	
	If the rate of environmental change is fast, the distribution of adaptive substitution mirrors the mutational distribution (Fig. 6).
Selectional correlation	
	If the rate of environmental change is slow, the distribution of adaptive substitution reflects the shape of the fitness landscape. (Fig. 6)

5. Supporting Information

In the following Supporting Information, we derive several analytical results for the adaptive-walk approximation.

5.1. Supporting Information 1: The selection coefficient

Figure S1_1 illustrates the time dependence of the selection coefficient $s(\mathbf{x}, \mathbf{y}, t)$ in the multi-dimensional moving-optimum model. Recall that $s(\mathbf{x}, \mathbf{y}, t)$ can be written as

$$s(\mathbf{x}, \mathbf{y}, t) \approx \lambda_{\mathbf{x},\mathbf{y}} \left(t - \tau_{\mathbf{x},\mathbf{y}} \right), \tag{S1a}$$

with

$$\lambda_{\mathbf{x},\mathbf{y}} = 2(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} \mathbf{v} \tag{S1b}$$

$$\tau_{\mathbf{x},\mathbf{y}} = \frac{(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} (\mathbf{x} + \mathbf{y})}{2(\mathbf{x} - \mathbf{y})' \boldsymbol{\Sigma}^{-1} \mathbf{v}}, \tag{S1c}$$

(provided $\lambda_{\mathbf{x},\mathbf{y}} \neq 0$), where $\lambda_{\mathbf{x},\mathbf{y}}$ is the rate of change and $\tau_{\mathbf{x},\mathbf{y}}$ is the lag time (i.e., the time when s reaches zero). The line $\lambda_{\mathbf{x},\mathbf{y}} = 0$ contains all mutational effects $\boldsymbol{\alpha}$ that are orthogonal to $\boldsymbol{\Sigma}^{-1}\mathbf{v}$, which in the case of uncorrelated selection ($\rho_\Sigma = 0$) simply means orthogonal to the direction of the moving optimum. Accordingly, the line divides the space of mutant phenotypes into "backward mutations" ($\lambda_{\mathbf{x},\mathbf{y}} < 0$), which have a chance at fixation only during a limited time window (if any), and "forward mutations", which have an unlimited amount of time to appear and go on to fixation. The set of mutations that are beneficial at time t is given by an ellipse (the solution of $s(\mathbf{x}, \mathbf{y}, t) = 0$) that passes through the wild-type $\mathbf{y}$ and has its center at the current optimum $\mathbf{v}t$. Note that, as the optimum moves on, the area of this ellipse decreases as long as the optimum is to the left of the $\lambda_{\mathbf{x},\mathbf{y}} = 0$ line, and increases indefinitely afterwards. Together with the $\lambda_{\mathbf{x},\mathbf{y}} = 0$ line, the two ellipses corresponding to the initial and the current optimum (bold and gray ellipse in Fig. S1_1, respectively) split the space of mutant phenotypes into six sectors: backward mutations that never were and never will be beneficial (sector **I**); backward mutations that were beneficial initially, but which have become deleterious by that time (sector **II**); backward mutations that are still beneficial (sector **III**); forward mutations that have been beneficial from the outset (sector **IV**); forward mutations that have become beneficial after a positive lag time $\tau_{\mathbf{x},\mathbf{y}}$ (sector **V**); and forward mutations that are not yet beneficial but will become beneficial in the future (sector **VI**). Note that,

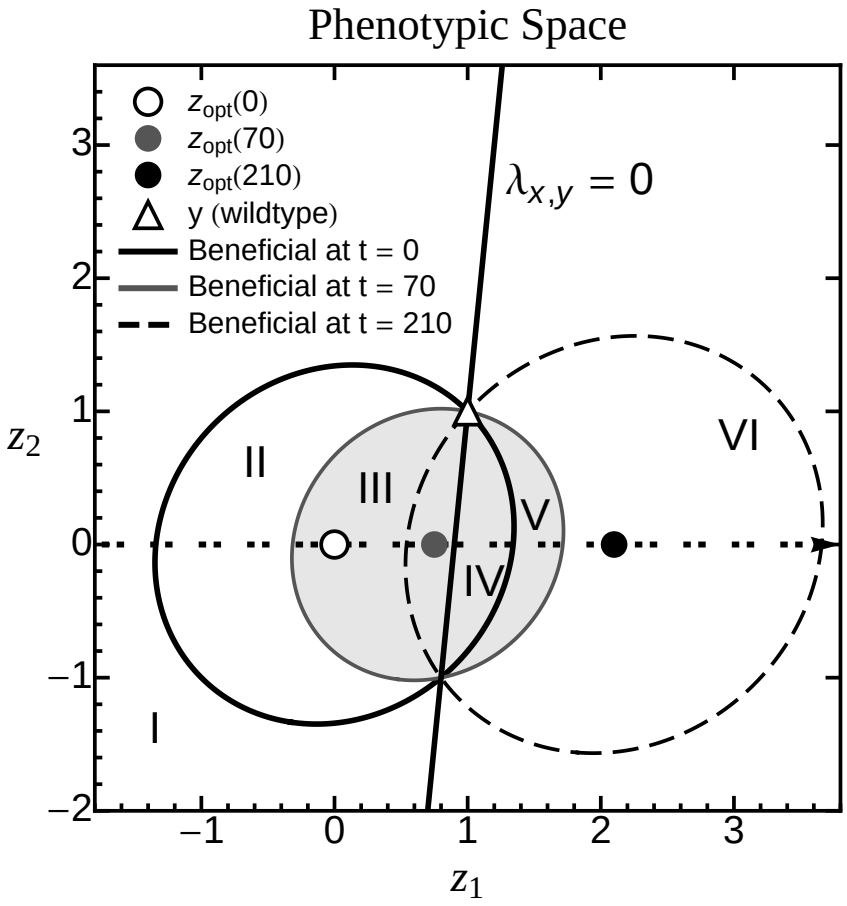

Figure S1_1 – The time dependence of selection in the two-dimensional moving optimum model. The axes span the values of two quantitative traits. The wildtype phenotype combination $\mathbf{y}$ is represented by the open triangle, and the optimum $\mathbf{z}_{\text{opt}}$ has moved at constant speed along the dotted line from the open circle at time $t = 0$ to the grey circle at time $t = 70$ and the black circle at time $t = 210$. The solid ellipse encloses the set of mutant phenotypes that were selectively favored at $t = 0$ (i.e., $\{\mathbf{x} \mid s(\mathbf{x}, \mathbf{y}, 0) > 0\}$), whereas the grey and the dashed ellipses represent those mutants that are selectively favored at $t = 70$ and $t = 210$, respectively ($\{\mathbf{x} \mid s(\mathbf{x}, \mathbf{y}, 70) > 0\}$). The solid line is the line $\lambda_{\mathbf{x},\mathbf{y}} = 0$, which divides the phenotype space into "forward" and "backward" types as described in the text. The roman numerals refer to sets of mutant phenotypes at time $t = 70$ that differ with respect to their past, present and future selection coefficient (see text for details). Parameters: $v_1 = 0.01, \Theta = 2, \sigma^2 = 10, \rho_\Sigma = 0.1$.

as the optimum moves on, sectors **II** and **V** will grow, sectors **III** and **VI** will shrink, and sectors **I** and **IV** remain unchanged.

5.2. Supporting Information 2: Transformation of phenotype space

To make further progress, we introduce a transformation of the phenotype space, which will be denoted by tildes ($\tilde{\mathbf{z}}$ etc.) and has the following properties: (i) the selection matrix $\tilde{\mathbf{\Sigma}}$ is proportional to the identity matrix, that is, selection is equally strong in all directions (isotropic); (ii) the optimum moves in the direction of the first trait axis, $\tilde{\mathbf{v}} = (\tilde{v}_1, 0, \ldots)'$, that is, only the first trait is under moving-optimum selection, whereas all other traits

are under constant stabilizing selection; (iii) the mutation matrix $\tilde{\mathbf{M}}$ has determinant 1; if mutation is uncorrelated in the transformed space, this means that the geometric mean of the mutational standard deviations equals 1; therefore, the length scale is determined by the average size of new mutations. According to these goals, the transformation is done in three steps. First, let $\mathbf{A}$ be the matrix whose rows contain the eigenvectors of $\boldsymbol{\Sigma}$, scaled to magnitude 1, and let $\mathbf{D}$ be the diagonal matrix containing the corresponding eigenvalues (i.e., $\boldsymbol{\Sigma}^{-1} = \mathbf{A}'\mathbf{D}^{-1}\mathbf{A}$). For the first step of the transformation, we define

$$\mathbf{B} = \bar{\sigma}\mathbf{D}^{-1/2}\mathbf{A}, \tag{S2}$$

with $\bar{\sigma} = \sqrt[2n]{\det(\boldsymbol{\Sigma})}$ (eq. 3), such that $\det(\mathbf{B}) = 1$ and $\mathbf{B}'\mathbf{B} = \bar{\sigma}^2\boldsymbol{\Sigma}^{-1}$. Substituting $\mathbf{z}$ by $\mathbf{B}^{-1}\dot{\mathbf{z}}$, such that $\dot{\mathbf{z}} = \mathbf{B}\mathbf{z}$, $\dot{\mathbf{x}} = \mathbf{B}\mathbf{x}$, $\dot{\mathbf{y}} = \mathbf{B}\mathbf{y}$, $\dot{\mathbf{v}} = \mathbf{B}\mathbf{v}$ and using the fact that $\tilde{\boldsymbol{\Sigma}}^{-1} = (\mathbf{B}^{-1})'\boldsymbol{\Sigma}^{-1}\mathbf{B}^{-1} = \bar{\sigma}^{-2}\mathbf{I}$, the selection coefficient (eq. 8a) in the transformed phenotype space is given by

$$\dot{s}(\dot{\mathbf{x}}, \dot{\mathbf{y}}, t) = \bar{\sigma}^{-2}\left(||\dot{\mathbf{y}} - \dot{\mathbf{v}}t||^2 - ||\dot{\mathbf{x}} - \dot{\mathbf{v}}t||^2\right) \tag{S3}$$

where $||\xi||^2 = \xi'\xi$ is the square of the Euclidean norm. After this first transformation step, goal (i) has been reached, that is, selection is symmetric in all directions with strength $\bar{\sigma}^{-2}$. For the second step, we need to define a $n \times n$ rotation matrix $\mathbf{R}$ that satisfies $\mathbf{R}\dot{\mathbf{v}} = (||\dot{\mathbf{v}}||, 0, \ldots, 0)'$. For the present calculation, it is not necessary to give $\mathbf{R}$ explicitly. However, for numerical calculations, such a matrix can always been found by applying the Gram-Schmidt orthonormalization algorithm (and a potential step of rearrangement) to a basis of the unrotated vector space that is given by the $n \times n$ identity matrix whose i^{th} column is replaced by $\dot{\mathbf{v}}$, where i is determined by the first non-zero entry of $\dot{\mathbf{v}}$. Like all rotation matrices, $\mathbf{R}$ satisfies $\mathbf{R}' = \mathbf{R}^{-1}$ and $\det(\mathbf{R}) = 1$. With the transformations $\ddot{\mathbf{z}} = \mathbf{R}\dot{\mathbf{z}}$ etc., we get

$$\ddot{s}(\ddot{\mathbf{x}}, \ddot{\mathbf{y}}, t) = \bar{\sigma}^{-2}\left(||\ddot{\mathbf{y}} - \ddot{\mathbf{v}}t||^2 - ||\ddot{\mathbf{x}} - \ddot{\mathbf{v}}t||^2\right). \tag{S4}$$

The third step of the transformation is to express all vectors relative to $\bar{m} = \sqrt[2n]{\det(\mathbf{M}^{-1})}$ (eq. 5), that is, $\tilde{\mathbf{z}} = \ddot{\mathbf{z}}/\bar{m}$ etc., leading to

$$\tilde{s}(\tilde{\mathbf{x}}, \tilde{\mathbf{y}}, t) = \bar{\tilde{\sigma}}^{-2}\left(||\tilde{\mathbf{y}} - \tilde{\mathbf{v}}t||^2 - ||\tilde{\mathbf{x}} - \tilde{\mathbf{v}}t||^2\right). \tag{S5}$$

with $\bar{\tilde{\sigma}} = \bar{\sigma}/\bar{m}$. Summarizing, we can combine all three steps by defining a transformation matrix

$$\mathbf{Q} = \frac{1}{\bar{m}}\mathbf{RB} = \bar{\tilde{\sigma}}\mathbf{RD}^{-1/2}\mathbf{A}, \tag{S6}$$

with $\det(\mathbf{Q}) = \bar{m}^{-n} = \sqrt{\det(\mathbf{M}^{-1})}$, such that $\tilde{\mathbf{z}} = \mathbf{Q}\mathbf{z}$ etc. Note that the transformation also affects the distribution of new mutations $\tilde{p}(\tilde{\boldsymbol{\alpha}})$, which is given by $\tilde{p}(\tilde{\boldsymbol{\alpha}}) = \det(\mathbf{Q}^{-1}) \cdot p(\mathbf{Q}^{-1}\tilde{\boldsymbol{\alpha}}) = \bar{m}^n p(\boldsymbol{\alpha})$, and has covariance matrix $\tilde{\mathbf{M}} = \mathbf{Q}\mathbf{M}\mathbf{Q}'$ with $\det(\tilde{\mathbf{M}}) = 1$.

5.3. Supporting Information 3: The parameter γ

We can use the transformation from Supporting Information 2 to show that the parameters Θ, $\mathbf{v}$ and $\boldsymbol{\Sigma}$ affect the distribution of adaptive substitutions only through the composite parameter γ.

First, using the fact that $\tilde{\mathbf{v}} = (\tilde{v}_1, 0, \ldots)'$, $g(t, \mathbf{y})$ (eq. 9) can be rewritten as

$$\tilde{g}(t, \tilde{\mathbf{y}}) = \Theta\bar{\tilde{\sigma}}^{-2} \int_{\tilde{\chi}} \tilde{p}(\tilde{\boldsymbol{\alpha}}) \left[2(\tilde{x}_1 - \tilde{y}_1)'\tilde{v}_1 t - (\tilde{\mathbf{x}}'\tilde{\mathbf{x}} - \tilde{\mathbf{y}}'\tilde{\mathbf{y}})\right] d\tilde{\mathbf{x}}, \tag{S7}$$

where the integration region $\tilde{\chi}(t, \tilde{\mathbf{y}}) = \{\tilde{\mathbf{x}} \mid \|\tilde{\mathbf{x}} - \tilde{\mathbf{v}}t\| < \|\tilde{\mathbf{y}} - \tilde{\mathbf{v}}t\|\}$ is the set of mutant phenotypes in the transformed space with positive selection coefficient at time t. Next, using the substitution $\zeta = \tilde{v}_1 t$, the waiting-time distribution on the transformed scale, $\tilde{F}(t|\tilde{\mathbf{y}}) = \exp\left(-\int_0^t \tilde{g}(\tau, \tilde{\mathbf{y}})d\tau\right)$ (eq. 10) can be written as

$$\tilde{F}(t|\tilde{\mathbf{y}}) = \exp\left(-\frac{1}{\gamma}\int_0^{\tilde{v}_1 t} \int_{\tilde{\chi}} \tilde{p}(\tilde{\boldsymbol{\alpha}}) \left[2(\tilde{x}_1 - \tilde{y}_1)'\zeta - (\tilde{\mathbf{x}}'\tilde{\mathbf{x}} - \tilde{\mathbf{y}}'\tilde{\mathbf{y}})\right] d\tilde{\mathbf{x}} d\zeta\right) \tag{S8}$$

with

$$\gamma = \frac{\tilde{v}_1}{\Theta\tilde{\sigma}^{-2}}. \tag{S9}$$

Therefore, $\tilde{F}(t|\tilde{\mathbf{y}})$ depends only on γ, $\tilde{p}$ (or $\tilde{\mathbf{M}}$), $\tilde{\mathbf{y}}$, and the product $\tilde{v}_1 t$. Furthermore, the same substitution can be applied to the distribution of adaptive substitutions, which can be written as

$$\tilde{\phi}(\tilde{\boldsymbol{\alpha}}|\tilde{\mathbf{y}}) = \frac{\tilde{p}(\tilde{\boldsymbol{\alpha}})}{\gamma} \int_{\frac{\tilde{\mathbf{x}}'\tilde{\mathbf{x}} - \tilde{\mathbf{y}}'\tilde{\mathbf{y}}}{2(\tilde{x}_1 - \tilde{y}_1)}}^{\infty} \left[2(\tilde{x}_1 - \tilde{y}_1)\zeta - (\tilde{\mathbf{x}}'\tilde{\mathbf{x}} - \tilde{\mathbf{y}}'\tilde{\mathbf{y}})\right] \tilde{F}(\zeta|\tilde{\mathbf{y}}) d\zeta. \tag{S10}$$

Thus, in the transformed space, the distribution of adaptive substitutions depends only on γ, the initial phenotype $\tilde{\mathbf{y}}$, and the distribution of new mutations $\tilde{p}(\tilde{\boldsymbol{\alpha}})$. At the original scale, we have $\phi(\boldsymbol{\alpha}|\mathbf{y}) = \det(\mathbf{Q})\tilde{\phi}(\tilde{\boldsymbol{\alpha}}|\tilde{\mathbf{y}}) = \bar{m}^{-n}\tilde{\phi}(\mathbf{Q}\boldsymbol{\alpha}|\mathbf{Q}\mathbf{y})$. Finally, since

$$\tilde{v}_1 = \|\tilde{\mathbf{v}}\| = \frac{1}{\bar{m}}\|\mathbf{B}\mathbf{v}\| = \frac{1}{\bar{m}}\sqrt{\mathbf{v}'\mathbf{B}'\mathbf{B}\mathbf{v}} = \bar{\tilde{\sigma}}\sqrt{\mathbf{v}'\boldsymbol{\Sigma}^{-1}\mathbf{v}}, \tag{S11}$$

γ reduces to the form given in equation (13) of the main text when expressed in terms of the original variables.

In the adaptive-walk approximation, the effects of the rate and direction of environmental change $\mathbf{v}$, the population-wide mutation rate Θ and the selection matrix $\boldsymbol{\Sigma}$ are completely captured by γ. The same is, however, not true for changes in the mutational covariance matrix $\mathbf{M}$ (and, hence, the distribution of new mutations $p(\boldsymbol{\alpha})$; see eq. S10), since γ contains only the "average variance" of mutational effects ($\bar{m}^2$, eq. 5), but not the details of the correlation structure. γ also does not capture the impact of organismic complexity *per se*, as it is independent of n in the absence of mutational and selectional correlations (eq. 14). In the presence of correlations, γ may depend on n, but only because $\bar{\sigma}$ or $\bar{m}$ depend on n. For example, increasing the number of selectionally correlated traits increases the average strength of selection, and hence decreases $\bar{\sigma}$ (eq. 3).

Kopp and Hermisson (2009b) proposed a value of $\gamma \ll 1$ as an approximate boundary between the environmentally- and genetically-limited regimes. In the context of the present paper, a value of $\gamma = 1$ is already very large and often leads to population extinction in individual-based simulations. Indeed, it refers to a situation where the adaptive process is clearly neither environmentally nor genetically limited. For $n = 1$, the environmental limit (where the distribution of new mutations can be treated as effectively uniform) provides a very good approximation for $\gamma \lesssim 10^{-2} - 10^{-1}$ (see Fig. 4F Kopp and Hermisson 2009b). Here, we show that this boundary shifts to smaller values as complexity increases (reflecting the cost of complexity, see above), but the approximation remains reasonably good for $\gamma = 10^{-2}$ (Fig. S5_1, S5_2, S5_3). In general, for the mean step size in the direction of the optimum ($\bar{\alpha}_1$), the relative error incurred by the approximation remains at the order of 10% as long as the mean step size is on the order of magnitude of the (mean) standard deviation of the effects of new mutations ($\bar{\alpha}_1 \approx \bar{m}$, see Fig S5_2). Similarly, in Fig. 6, the effects of mutational and selectional correlations offset each other (indicating an intermediate regime) around $\gamma = 0.1$ ($v_1 \approx 0.005$).

5.4. Supporting Information 4: The environmentally-limited regime (uniform distribution of new mutations)

As argued in the main text, if γ is sufficiently small, the distribution of new mutations $p(\boldsymbol{\alpha})$ can be approximated by a uniform distribution with $p_u(\boldsymbol{\alpha}) = p(\mathbf{0}) \equiv p_0$. This simplification allows further analytical progress. For the instantaneous rate of fixation, $\tilde{g}(t, \tilde{\mathbf{y}})$

(eq. S7), we can use the fact that, in the transformed phenotype space, all mutants with a given distance $\tilde{r} = ||\tilde{\mathbf{x}} - \tilde{\mathbf{v}}t||$ from the optimum have identical selection coefficients

$$\tilde{s}(\tilde{r}, \tilde{\mathbf{y}}, t) = \tilde{\bar{\sigma}}^{-2}\left(\tilde{\delta}(t, \tilde{\mathbf{y}})^2 - \tilde{r}^2\right), \quad \text{for } \tilde{r} < \tilde{\delta}(t, \tilde{\mathbf{y}}) \tag{S12}$$

where we denote by $\tilde{\delta}(t, \tilde{\mathbf{y}}) = ||\tilde{\mathbf{y}} - \tilde{\mathbf{v}}t||$ the distance of the wild-type from the optimum at time t.

The weight of such a class of mutants is given by the surface $S_n(\tilde{r})$ of a n-dimensional hypersphere with radius $\tilde{r}$ (Hartl and Taubes 1998; Tenaillon et al. 2007; Gros et al. 2009), which is

$$S_n = \frac{2\pi^{\frac{n}{2}}}{\Gamma\left(\frac{n}{2}\right)}\tilde{r}^{n-1}, \tag{S13}$$

where $\Gamma(\bullet)$ denotes the gamma function. $\tilde{g}(t, \tilde{\mathbf{y}})$ is then given by

$$\begin{aligned}\tilde{g}(t, \tilde{\mathbf{y}}) &= \Theta\tilde{p}_0 \int_0^{\tilde{\delta}(t,\tilde{\mathbf{y}})} S_n(\tilde{r}) s(\tilde{r}, \tilde{\mathbf{y}}, t) d\tilde{r} \\ &= \Theta\tilde{p}_0 \tilde{\bar{\sigma}}^{-2} \frac{2\pi^{\frac{n}{2}}}{\Gamma\left(\frac{n}{2}\right)} \int_0^{\tilde{\delta}(t,\tilde{\mathbf{y}})} \tilde{r}^{n-1}\left(\tilde{\delta}(t, \tilde{\mathbf{y}})^2 - \tilde{r}^2\right) d\tilde{r} \\ &= \Theta\tilde{p}_0 \tilde{\bar{\sigma}}^{-2} \frac{\pi^{\frac{n}{2}}}{\Gamma\left(2 + \frac{n}{2}\right)} \tilde{\delta}(t, \tilde{\mathbf{y}})^{n+2},\end{aligned} \tag{S14}$$

where we used the fact that $\xi\Gamma(\xi) = \Gamma(\xi + 1)$. Here, $\tilde{p}_0 = \det(\mathbf{Q}^{-1})p_0 = \bar{m}^n p_0$. For a general wild-type phenotype $\mathbf{y}$, the waiting-time distribution is given by

$$\tilde{F}(t|\tilde{\mathbf{y}}) = \exp\left(-\int_0^t \tilde{g}(\tau, \tilde{\mathbf{y}}) d\tau\right) = \exp\left(-\frac{\tilde{p}_0}{\gamma} \frac{\pi^{\frac{n}{2}}}{\Gamma\left(2 + \frac{n}{2}\right)} \tilde{\nu}_1 \int_0^t ||\tilde{\nu}_1\tau - \tilde{\mathbf{y}}||^{n+2} d\tau\right). \tag{S15}$$

The integral in the exponent can be easily calculated for even values of n, and (e.g., by using *Mathematica*) also for small odd n, but the resulting expressions are unwieldy and will not be given here. We note that adaptive walks in the environmentally-limited regime can be efficiently simulated by alternately drawing the step time from the distribution (S15) and the step size from the conditional distribution (11). (For the latter, use the symmetry of the transformed trait space by first drawing the new distance from the optimum, $\tilde{r}$ [see (S14)], and then choosing a random direction.)

Characterization of the first step of the adaptive walk in the environmentally-limited case. Further progress can be made if the wild-type is initially well-adapted ($\mathbf{y} = \mathbf{0}$), such that $\tilde{\delta}(t, \tilde{\mathbf{y}}) = \tilde{v}_1 t$. We refer to the adaptive substitution with these initial conditions as the first step of the adaptive walk. The waiting-time distribution for this step simplifies to

$$\tilde{F}(t|\mathbf{0}) = \exp\left(-\frac{\tilde{p}_0}{\gamma}\eta(n)(\tilde{v}_1 t)^{n+3}\right) \tag{S16}$$

with

$$\eta(n) = \frac{\pi^{\frac{n}{2}}}{(n+3)\Gamma\left(2+\frac{n}{2}\right)}. \tag{S17}$$

Below, we will use the moments of the waiting-time distribution, which are given by

$$\mathrm{E}(t^i|\mathbf{0}) = \int_0^\infty t^i \tilde{f}(t|\mathbf{0})dt = \frac{1}{\tilde{v}_1^i}\left(\frac{\gamma}{\eta(n)\tilde{p}_0}\right)^{\frac{i}{n+3}}\Gamma\left(\frac{n+3+i}{n+3}\right), \quad i = 1, 2, \ldots. \tag{S18}$$

Using equations (S1) and (12b), the distribution of the first adaptive step can be expressed as

$$\begin{aligned}\tilde{\phi}(\tilde{\boldsymbol{\alpha}}|\mathbf{0}) &= \lambda_{\tilde{\boldsymbol{\alpha}},\mathbf{0}}\tau^2_{\tilde{\boldsymbol{\alpha}},\mathbf{0}}\left(\mathbf{E}_{\frac{1+n}{3+n}}\left(\frac{\eta(n)\tilde{p}_0}{\gamma}\left(\tilde{v}_1\tau_{\tilde{\boldsymbol{\alpha}},\mathbf{0}}\right)^{n+3}\right) - \mathbf{E}_{\frac{2+n}{3+n}}\left(\frac{\eta(n)\tilde{p}_0}{\gamma}\left(\tilde{v}_1\tau_{\tilde{\boldsymbol{\alpha}},\mathbf{0}}\right)^{n+3}\right)\right)\\ &= \frac{\tilde{p}_0}{(n+3)\gamma}\frac{||\tilde{\boldsymbol{\alpha}}||^4}{2\tilde{\alpha}_1}\left(\mathbf{E}_{\frac{1+n}{3+n}}\left(\frac{\eta(n)\tilde{p}_0}{\gamma}\left[\frac{||\tilde{\boldsymbol{\alpha}}||^2}{2\tilde{\alpha}_1}\right]^{n+3}\right) - \mathbf{E}_{\frac{2+n}{3+n}}\left(\frac{\eta(n)\tilde{p}_0}{\gamma}\left[\frac{||\tilde{\boldsymbol{\alpha}}||^2}{2\tilde{\alpha}_1}\right]^{n+3}\right)\right),\end{aligned} \tag{S19}$$

where $\mathbf{E}_\xi(\psi) = \int_1^\infty (\exp(-\psi t)/t^\xi)dt$ denotes the exponential integral function.

While this expression is not particularly instructive, further insight can be gained by focusing on the moments of the distributions of certain components of $\tilde{\boldsymbol{\alpha}}$.

Distribution of $\tilde{\alpha}_1$. We start by deriving the moments of the marginal distribution of step sizes in the direction of the optimum, which we will denote by $\tilde{\phi}_1(\tilde{\alpha}_1)$. Here and below, our strategy will be to first focus on the conditional distribution of step sizes given the waiting time (eq. 11), which in the transformed trait space, is given by

$$\tilde{\phi}(\tilde{\boldsymbol{\alpha}}|t,\mathbf{0}) = \frac{\Theta\tilde{p}_0 s(\tilde{\boldsymbol{\alpha}},\mathbf{0},t)}{\tilde{g}(t,\mathbf{0})} = \frac{2\tilde{\alpha}_1\tilde{v}_1 t - \|\tilde{\boldsymbol{\alpha}}\|^2}{\frac{\pi^{n/2}}{\Gamma\left(2+\frac{n}{2}\right)}(\tilde{v}_1 t)^{n+2}}. \tag{S20}$$

Accordingly, the conditional distribution of $\tilde{\alpha}_1$ is

$$\begin{aligned}\tilde{\phi}_1(\tilde{\alpha}_1|t,\mathbf{0}) &= \int_0^{\sqrt{2\tilde{\alpha}_1\tilde{v}_1 t-\tilde{\alpha}_1^2}} S_{n-1}(\tilde{r})\tilde{\phi}[(\tilde{\alpha}_1,\tilde{r},0,\ldots)'|t,\mathbf{0}]d\tilde{r} \\ &= \frac{2}{(\tilde{v}_1 t)^{n+2}}\frac{\Gamma\left(\frac{n+4}{2}\right)}{\sqrt{\pi}\Gamma\left(\frac{n-1}{2}\right)}\int_0^{\sqrt{2\tilde{\alpha}_1\tilde{v}_1 t-\tilde{\alpha}_1^2}}(2\tilde{\alpha}_1\tilde{v}_1 t-\tilde{\alpha}_1^2-\tilde{r}^2)\tilde{r}^{n-2}d\tilde{r} \\ &= \frac{4}{(n^2-1)(\tilde{v}_1 t)^{n+2}}\frac{\Gamma\left(\frac{n+4}{2}\right)}{\sqrt{\pi}\,\Gamma\left(\frac{n-1}{2}\right)}(2\tilde{\alpha}_1\tilde{v}_1 t-\tilde{\alpha}_1^2)^{\frac{n+1}{2}},\end{aligned} \tag{S21}$$

where the integration is over all classes of mutations with identical fitness. Using Mathematica, the i'th moment of this conditional distribution can be evaluated to

$$\mathrm{E}(\tilde{\alpha}_1^i|t,\mathbf{0}) = \int_0^{2\tilde{v}_1 t}\tilde{\alpha}_1^i\,\tilde{\phi}_1(\tilde{\alpha}_1|t,\mathbf{0})d\tilde{\alpha}_1 = \frac{2^i\Gamma(n+3)\Gamma\left(\frac{n+3+2i}{2}\right)}{\Gamma(n+3+i)\Gamma\left(\frac{n+3}{2}\right)}(\tilde{v}_1 t)^i. \tag{S22}$$

By applying the properties of the Gamma function and cancelling, this can be simplified to

$$\mathrm{E}(\tilde{\alpha}_1^i|t,\mathbf{0}) = \begin{cases}(\tilde{v}_1 t)^i\prod_{j=1}^{i/2}\frac{n+1+i+2j}{n+2+2j} & \text{if } i \text{ is even,}\\ (\tilde{v}_1 t)^i\prod_{j=1}^{(i-1)/2}\frac{n+2+i+2j}{n+2+2j} & \text{if } i \text{ is odd.}\end{cases} \tag{S23}$$

In particular,

$$\mathrm{E}(\tilde{\alpha}_1|t,\mathbf{0}) = \tilde{v}_1 t, \tag{S24}$$

$$\mathrm{E}(\tilde{\alpha}_1^2|t,\mathbf{0}) = \frac{n+5}{n+4}(\tilde{v}_1 t)^2. \tag{S25}$$

The moments of the unconditional distribution are given by

$$\begin{aligned}\mathrm{E}(\tilde{\alpha}_1^i|\mathbf{0}) &= \int_0^\infty\tilde{\alpha}_1^i\left(\int_{\tilde{\alpha}_1/(2\tilde{v}_1)}^\infty\tilde{\phi}_1(\tilde{\alpha}_1|t,\mathbf{0})\tilde{f}(t|\mathbf{0})dt\right)d\tilde{\alpha}_1 \\ &= \int_0^\infty\tilde{f}(t|\mathbf{0})\left(\int_0^{2\tilde{v}_1 t}\tilde{\alpha}_1^i\,\tilde{\phi}_1(\tilde{\alpha}_1|t,\mathbf{0})d\tilde{\alpha}_1\right)dt.\end{aligned} \tag{S26}$$

The inner integral equals the conditional moment (eq. S22). Since the latter is proportional to t^i, the unconditional moment is simply

$$\mathrm{E}(\tilde{\alpha}_1^i|\mathbf{0}) = \frac{1}{t^i}\mathrm{E}(\tilde{\alpha}_1^i|t,\mathbf{0})\,\mathrm{E}(t^i|\mathbf{0}). \tag{S27}$$

For the ease of notation, t denotes a random variable as well as its realization. In particular,

$$\mathrm{E}(\tilde{\alpha}_1|\mathbf{0}) = \left(\frac{\gamma}{\eta(n)\tilde{p}_0}\right)^{\frac{1}{n+3}}\Gamma\left(\frac{n+4}{n+3}\right) \tag{S28}$$

$$\mathrm{Var}(\tilde{\alpha}_1|\mathbf{0}) = \mathrm{E}(\tilde{\alpha}_1^2|\mathbf{0}) - (\mathrm{E}(\tilde{\alpha}_1|\mathbf{0}))^2 = \left(\frac{\gamma}{\eta(n)\tilde{p}_0}\right)^{\frac{2}{n+3}}\left[\frac{n+5}{n+4}\Gamma\left(\frac{n+5}{n+3}\right) - \Gamma\left(\frac{n+4}{n+3}\right)^2\right]. \tag{S29}$$

As a consequence, the coefficient of variation $\sqrt{\mathrm{Var}(\tilde{\alpha}_1|\mathbf{0})}/\mathrm{E}(\tilde{\alpha}_1|\mathbf{0})$ is independent of γ, η and $\tilde{p}_0$. For the isotropic case, equations (16) and (17) in the main text are obtained by using $\tilde{p}_0 = (2\pi)^{-\frac{n}{2}}$ and transforming back to the original scale with $\boldsymbol{\alpha} = \mathbf{Q}^{-1}\tilde{\boldsymbol{\alpha}} = \bar{m}\tilde{\boldsymbol{\alpha}}$.

Distribution of $\tilde{\alpha}_2$. A similar calculation leads to the moments of the distribution of $\tilde{\alpha}_2$, or indeed of any trait under constant stabilizing selection (i.e., orthogonal to the direction of the moving optimum).

The conditional distribution of $\tilde{\alpha}_2$ is given by

$$\begin{aligned}\tilde{\phi}_2(\tilde{\alpha}_2|t,\mathbf{0}) &= \int_0^{\sqrt{(\tilde{v}_1 t)^2 - \tilde{\alpha}_2^2}} S_{n-1}(\tilde{r})\tilde{\phi}[(\tilde{v}_1 t + \tilde{r}, \tilde{\alpha}_2, 0, \ldots)'|t,\mathbf{0}]d\tilde{r} \\ &= \frac{4}{(n^2-1)(\tilde{v}_1 t)^{n+2}}\frac{\Gamma\left(\frac{n+4}{2}\right)}{\sqrt{\pi}\Gamma\left(\frac{n+1}{2}\right)}[(\tilde{v}_1 t)^2 - \tilde{\alpha}_2^2]^{\frac{n+1}{2}},\end{aligned} \tag{S30}$$

with moments

$$\begin{aligned}\mathrm{E}(\tilde{\alpha}_2^i|t,\mathbf{0}) &= \frac{[1+(-1)^i]\Gamma\left(\frac{1+i}{2}\right)\Gamma\left(\frac{n+4}{2}\right)}{2\sqrt{\pi}\,\Gamma\left(\frac{n+4+i}{2}\right)}(\tilde{v}_1 t)^i \\ &= \begin{cases}\prod_{j=1}^{i/2}\frac{(2j-1)}{(n+2+2j)}(\tilde{v}_1 t)^i & \text{if } i \text{ is even,} \\ 0 & \text{if } i \text{ is odd.}\end{cases}\end{aligned} \tag{S31}$$

The unconditional moments are again given by

$$\mathrm{E}(\tilde{\alpha}_2^i|\mathbf{0}) = \frac{1}{t^i}\mathrm{E}(\tilde{\alpha}_2^i|t,\mathbf{0})\,\mathrm{E}(t^i,\mathbf{0}). \tag{S32}$$

In particular, the variance of $\tilde{\alpha}_2$ is

$$\mathrm{Var}(\tilde{\alpha}_2|\mathbf{0}) = \mathrm{E}(\tilde{\alpha}_2^2|\mathbf{0}) = \frac{1}{n+4}\left(\frac{\gamma}{\eta(n)\tilde{p}_0}\right)^{\frac{2}{n+3}}\Gamma\left(\frac{n+5}{n+3}\right). \tag{S33}$$

Furthermore, due to symmetry, all pairs of components of $\tilde{\boldsymbol{\alpha}}$ are uncorrelated (though not independent). Hence, the covariance matrix of $\tilde{\boldsymbol{\alpha}}$ is a diagonal matrix with its first entry given by the right-hand side of equation (S29) and all others by the right-hand side of equation (S33). Furthermore, the covariance matrix in the untransformed space can be obtained from the back-transformation

$$\mathbf{Cov}(\boldsymbol{\alpha}|\mathbf{0}) = \mathbf{Q}^{-1}\mathbf{Cov}(\tilde{\boldsymbol{\alpha}}|\mathbf{0})(\mathbf{Q}^{-1})'. \tag{S34}$$

For the special case of selectional correlation discussed in the main text, one finds that, for $n = 2$

$$\mathbf{Cov}(\boldsymbol{\alpha}|\mathbf{0}) = \frac{1}{\sqrt{1-\rho_\Sigma^2}}\begin{pmatrix}(1-\rho_\Sigma^2)\mathrm{Var}(\tilde{\alpha}_1|\mathbf{0}) + \rho_\Sigma^2\mathrm{Var}(\tilde{\alpha}_2|\mathbf{0}) & \rho_\Sigma\mathrm{Var}(\tilde{\alpha}_2|\mathbf{0}) \\ \rho_\Sigma\mathrm{Var}(\tilde{\alpha}_2|\mathbf{0}) & \mathrm{Var}(\tilde{\alpha}_2|\mathbf{0})\end{pmatrix} \tag{S35}$$

and, hence,

$$\rho_\alpha = \mathrm{Cor}(\alpha_1,\alpha_2|\mathbf{0}) = \rho_\Sigma\sqrt{\frac{\mathrm{Var}(\alpha_2|\mathbf{0})}{\mathrm{Var}(\alpha_1|\mathbf{0})}} \approx \rho_\Sigma\sqrt{(1-\rho_\Sigma^2)0.77 + \rho_\Sigma^2} \approx \rho_\Sigma. \tag{S36}$$

In particular, ρ_α (for the first step and in the environmentally-limited regime) is independent of γ.

Distribution of $\|\tilde{\boldsymbol{\alpha}}\|$. As shown by equation (S19), the distribution of adaptive substitutions depends only on the first component $\tilde{\alpha}_1$ and the total step size $\|\tilde{\boldsymbol{\alpha}}\|$ (i.e., of the Euclidean norm of $\tilde{\boldsymbol{\alpha}}$). To characterize the distribution of $\|\tilde{\boldsymbol{\alpha}}\|$, we again start with the conditional distribution, which can be written as

$$\tilde{\phi}_{\mathrm{norm}}(\|\tilde{\boldsymbol{\alpha}}\| \mid t,\mathbf{0}) = \int_{\frac{\|\tilde{\boldsymbol{\alpha}}\|^2}{2\tilde{v}_1 t}}^{\|\tilde{\boldsymbol{\alpha}}\|} S_{n-1}\left(\sqrt{\|\tilde{\boldsymbol{\alpha}}\|^2 - \tilde{\alpha}_1^2}\right)\tilde{\phi}\left[\left(\tilde{\alpha}_1,\sqrt{\|\tilde{\boldsymbol{\alpha}}\|^2-\tilde{\alpha}_1^2},0,\ldots\right)' \mid t,\mathbf{0}\right]\frac{\|\tilde{\boldsymbol{\alpha}}\|}{\sqrt{\|\tilde{\boldsymbol{\alpha}}\|^2-\tilde{\alpha}_1^2}}\,d\tilde{\alpha}_1. \tag{S37}$$

Here, the last term arises because the integral is calculated along a line in the $(\tilde{\alpha}_1, \tilde{\alpha}_2)$ space, where $\tilde{\alpha}_2 = \sqrt{\|\tilde{\boldsymbol{\alpha}}\|^2 - \tilde{\alpha}_1^2}$. After some rearrangements and using Mathematica, the moments of this distribution can be evaluated to yield

$$\mathrm{E}(\|\tilde{\boldsymbol{\alpha}}\|^i \mid t, \mathbf{0}) = \frac{2^{n+1+i}\Gamma\left(\frac{n+4}{2}\right)\Gamma\left(\frac{n+1+i}{2}\right)}{(n+2+i)\sqrt{\pi}/\Gamma\left(\frac{2n+2+i}{2}\right)}(\tilde{v}_1 t)^i, \tag{S38}$$

and the unconditional moments are again given by

$$\mathrm{E}(\|\tilde{\boldsymbol{\alpha}}\|^i|\mathbf{0}) = \frac{1}{t^i}\mathrm{E}(\|\tilde{\boldsymbol{\alpha}}\|^i \mid t, \mathbf{0})\,\mathrm{E}(t^i|\mathbf{0}). \tag{S39}$$

Again, the coefficient of variation is independent of γ, η and $\tilde{p}_0$.

Distribution of $\sqrt{\sum_{j=2}^n \tilde{\alpha}_j^2}$. We might also be interested in how much deviation from the optimum an adaptive substitution incurs in the traits under constant selection (this can be seen as the "cost" for following the moving optimum). Let this deviation be denoted by $\tilde{\epsilon} = \sqrt{\sum_{j=2}^n \tilde{\alpha}_j^2} = \sqrt{\|\tilde{\boldsymbol{\alpha}}\|^2 - \tilde{\alpha}_1^2}$. The conditional distribution of $\tilde{\epsilon}$ is

$$\begin{aligned}\tilde{\phi}_\epsilon(\epsilon|t, \mathbf{0}) &= \int_{\tilde{v}_1 t - \sqrt{(\tilde{v}_1 t)^2 - \tilde{\epsilon}^2}}^{\tilde{v}_1 t + \sqrt{(\tilde{v}_1 t)^2 - \tilde{\epsilon}^2}} S_{n-1}(\tilde{\epsilon})\tilde{\phi}[\tilde{\alpha}_1, \tilde{\epsilon}, 0, \ldots)'|t, \mathbf{0}]d\tilde{\alpha}_1 \\ &= \frac{8\,\Gamma\left(\frac{n+4}{2}\right)\epsilon^{n-2}\left((\tilde{v}_1 t)^2 - \epsilon^2\right)^{3/2}}{3(\tilde{v}_1 t)^{n+2}\sqrt{\pi}\,\Gamma\left(\frac{n-1}{2}\right)}.\end{aligned} \tag{S40}$$

Its moments are

$$\mathrm{E}(\tilde{\epsilon}^i|t, \mathbf{0}) = \frac{\Gamma\left(\frac{n+4}{2}\right)\Gamma\left(\frac{n-1+i}{2}\right)}{\Gamma\left(\frac{n-1}{2}\right)\Gamma\left(\frac{n+4+i}{2}\right)}(\tilde{v}_1 t)^i, \tag{S41}$$

and the unconditional moments are again $\mathrm{E}(\tilde{\epsilon}^i|\mathbf{0}) = t^{-i}\mathrm{E}(\tilde{\epsilon}^i|t, \mathbf{0})\mathrm{E}(t^i|\mathbf{0})$, with the coefficient of variation independent of γ, η and $\tilde{p}_0$. In addition, we can calculate the covariance between $\tilde{\alpha}_1$ and $\tilde{\epsilon}$. We start with the conditional expectation of the product $\tilde{\alpha}_1\tilde{\epsilon}$,

$$\begin{aligned}\mathrm{E}(\tilde{\alpha}_1\tilde{\epsilon}|t, \mathbf{0}) &= \int_0^{2\tilde{v}_1 t}\int_0^{\sqrt{2\tilde{\alpha}_1\tilde{v}_1 t - \alpha_1^2}} \tilde{\alpha}_1\tilde{\epsilon}S_{n-1}(\tilde{\epsilon})\tilde{\phi}((\tilde{\alpha}_1, \tilde{\epsilon}, 0, \ldots)|t, \mathbf{0})d\tilde{\epsilon}d\tilde{\alpha}_1 \\ &= \frac{(n+2)\Gamma\left(\frac{n+2}{2}\right)^2}{n\Gamma\left(\frac{n-1}{2}\right)\Gamma\left(\frac{n+5}{2}\right)}(\tilde{v}_1 t)^2.\end{aligned} \tag{S42}$$

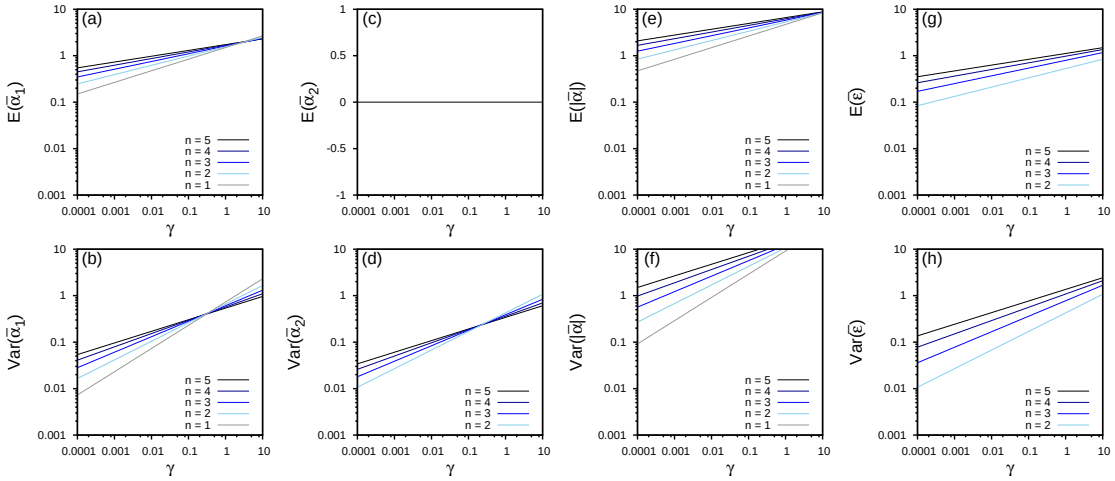

Figure S4_1 – Dependence of various components of the first adaptive step $\tilde{\boldsymbol{\alpha}}$ in the transformed phenotype space, as a function of the scaled rate of environmental change γ for various numbers of traits n, assuming a uniform distribution of new mutations. (a,b) Expectation and variance of the step size in the direction of the moving optimum, $\tilde{\alpha}_1$ (eq. S28 and S29); (c, d) expectation and variance of step size in an direction orthogonal to the moving optimum, $\tilde{\alpha}_1$ (eq. S33); (e, f) expectation and variance of the total step size (Euclidean norm), $\|\tilde{\boldsymbol{\alpha}}\|$ (based on eq. S39); (g, h) expectation and variance of the total deviation from the optimum in traits under constant stabilizing selection, $\tilde{\epsilon} = \sqrt{\sum_{j=2}^{n} \tilde{\alpha}_j^2}$ (based on eq. S41).

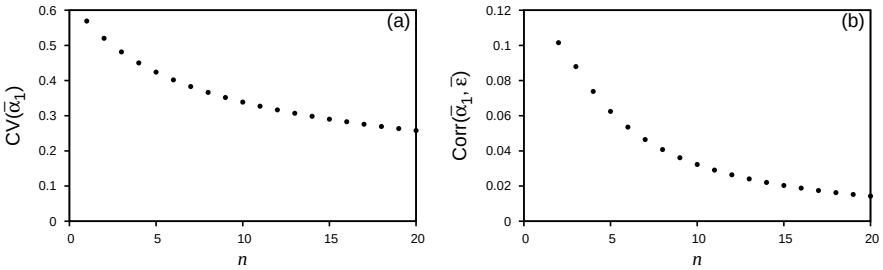

Figure S4_2 – (a) Coefficient of variation of the size of the first step in the direction of the moving optimum, $\sqrt{\mathrm{Var}(\tilde{\alpha}_1)}/\mathrm{E}(\tilde{\alpha}_1)$. (b) Correlation coefficient between the size of the first step in the direction of the moving optimum and its total deviation from the optimum in traits under constant stabilizing selection, $\rho(\tilde{\alpha_1}, \tilde{\epsilon})$ (eq. S44). Both quantities depend only on the number of traits, n. Results are valid in the transformed phenotype space and assume a uniform distribution of new mutations.

The unconditional expectation is $\mathrm{E}(\tilde{\alpha}_1\tilde{\epsilon}|\mathbf{0}) = \frac{1}{t^2}\mathrm{E}(\tilde{\alpha}_1\tilde{\epsilon}|\mathbf{0})\mathrm{E}(t^2|\mathbf{0})$, and the covariance is given by

$$\mathrm{Cov}(\tilde{\alpha}_1, \tilde{\epsilon}|\mathbf{0}) = \mathrm{E}(\tilde{\alpha}_1\tilde{\epsilon}|\mathbf{0}) - \mathrm{E}(\tilde{\alpha}_1|\mathbf{0})\mathrm{E}(\tilde{\epsilon}|\mathbf{0}). \tag{S43}$$

Furthermore, it is easy to show that the coefficient of correlation

$$\rho(\tilde{\alpha}_1, \tilde{\epsilon}|\mathbf{0}) = \frac{\mathrm{Cov}(\tilde{\alpha}_1, \tilde{\epsilon}|\mathbf{0})}{\sqrt{\mathrm{Var}(\tilde{\alpha}_1|\mathbf{0})\mathrm{Var}(\tilde{\epsilon}|\mathbf{0})}} \tag{S44}$$

is independent of γ, η and $\tilde{p}_0$.

An illustration of some of these results is give in Figure S4_1. Note that all quantities depend on γ only through the moments of the waiting-time distribution (eq. S18), whose power-law form leads to the linear relationship in double-log plots, with the slope for the i'th moment given by the exponent $i/(n + 3)$. Since this slope decreases with n (ultimately a geometric consequence of equation S13), the lines in Figure S4_1 cross at high values of γ. Biologically, this means that, while at a given distance to the optimum, the proportion of beneficial mutations is smaller in complex organisms, the same proportion increases faster as the distance to the optimum increases. As a consequence, at very high values of γ, the relationship between mean step size and n is reversed, with more complex organisms being predicted to evolve in smaller steps. However, this effect only sets in if the environment changes so fast that realistic populations cannot follow anyway and go extinct right away.

5.5. Supporting Information 5: Supplementary Figures

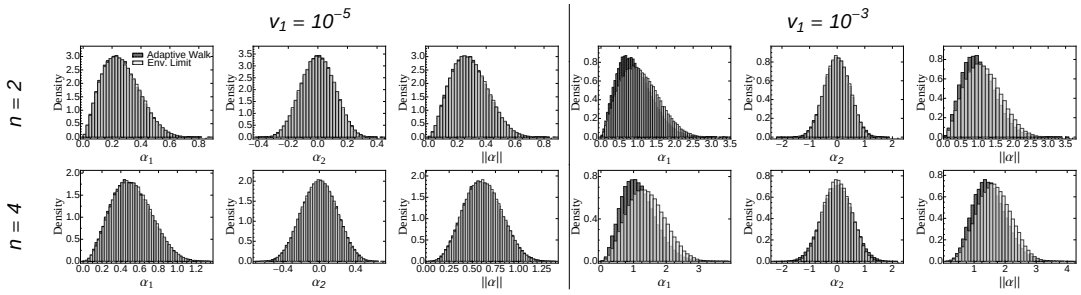

Figure S5_1 – Distribution of the size of the first adaptive substitution, for two (top row) and four (bottom row) traits and two different rates of environmental change v_1. For each rate, columns display the distribution of step sizes in direction of the moving optimum (α_1, left column), the distribution of step sizes for the trait under stabilizing selection (α_2, central column) and the distribution of the total step sizes ($||\boldsymbol{\alpha}||$, right column). Results are shown for adaptive-walk simulations (dark bins) assuming a normally-distributed distribution of new mutations and for the approximation eq. S19, which is based on a uniform distribution of new mutations (light bins). Note that the scales of the axes vary between plots. Parameters: $\Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0, m^2 = 1, \rho_M = 0$. Scaled rate of environmental change $\gamma = 10 \cdot v_1$.

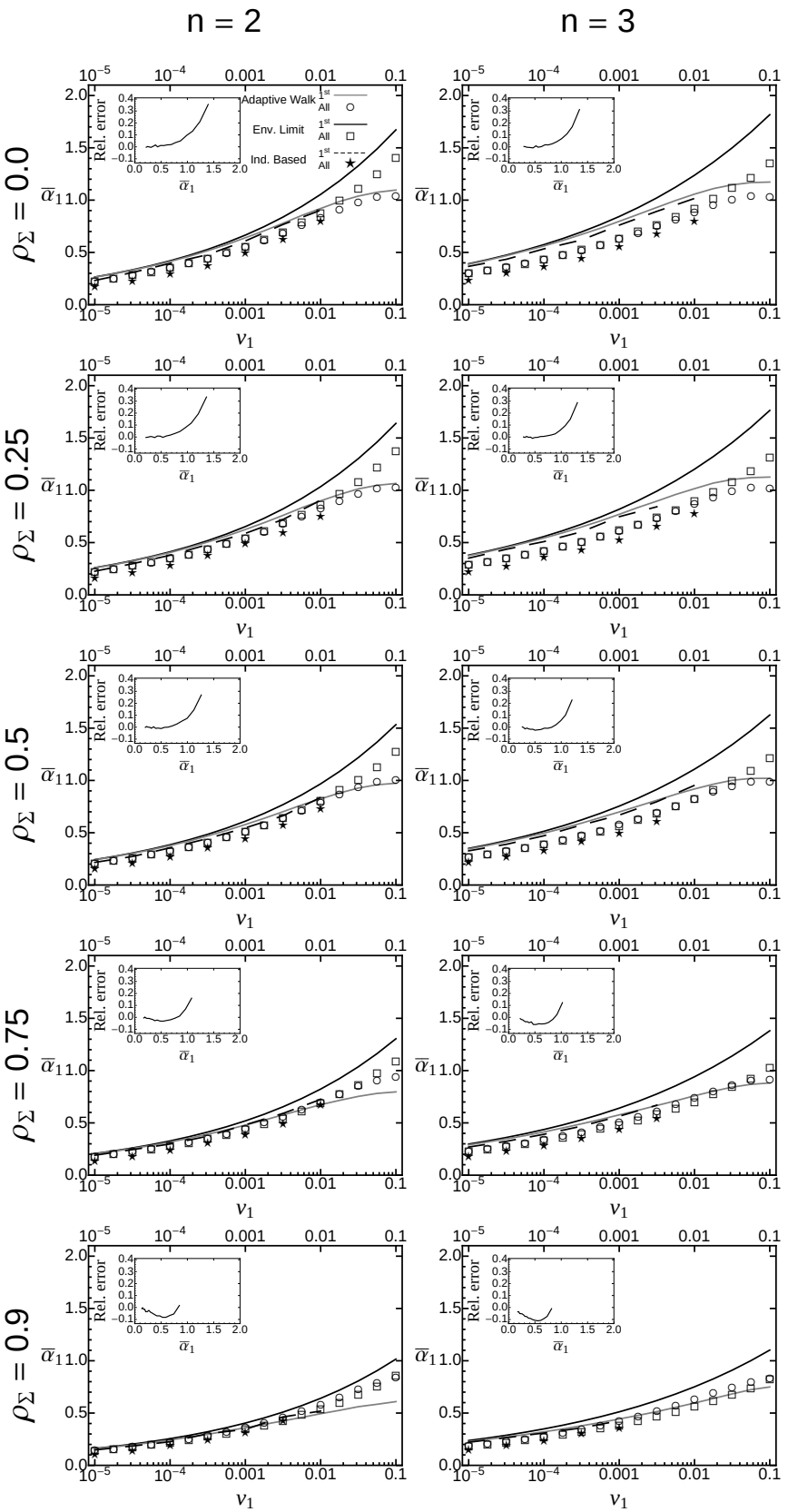

Figure S5_2 – Mean size $\tilde{\alpha}_1$ of adaptive substitutions in the direction of the moving optimum, for the first step (lines) and over the entire adaptive walk (symbols), as a function of the rate of environmental change v_1, for $n = 2$ and 3 traits and different values of selectional correlation ρ_Σ. "Adaptive walk" refers to adaptive-walk simulations with a normal distribution of new mutations, "Env. limit" to adaptive-walk simulations assuming a uniform distribution of new mutations (eq. S19), and "Ind. based" to individual-based simulations (with normally distributed new mutations). Also shown is the relative error over all steps incurred by "Env. limit" relative to "Adaptive walk". Parameters: $\Theta = 1, \sigma^2 = 10, m^2 = 1, \rho_M = 0.0$.

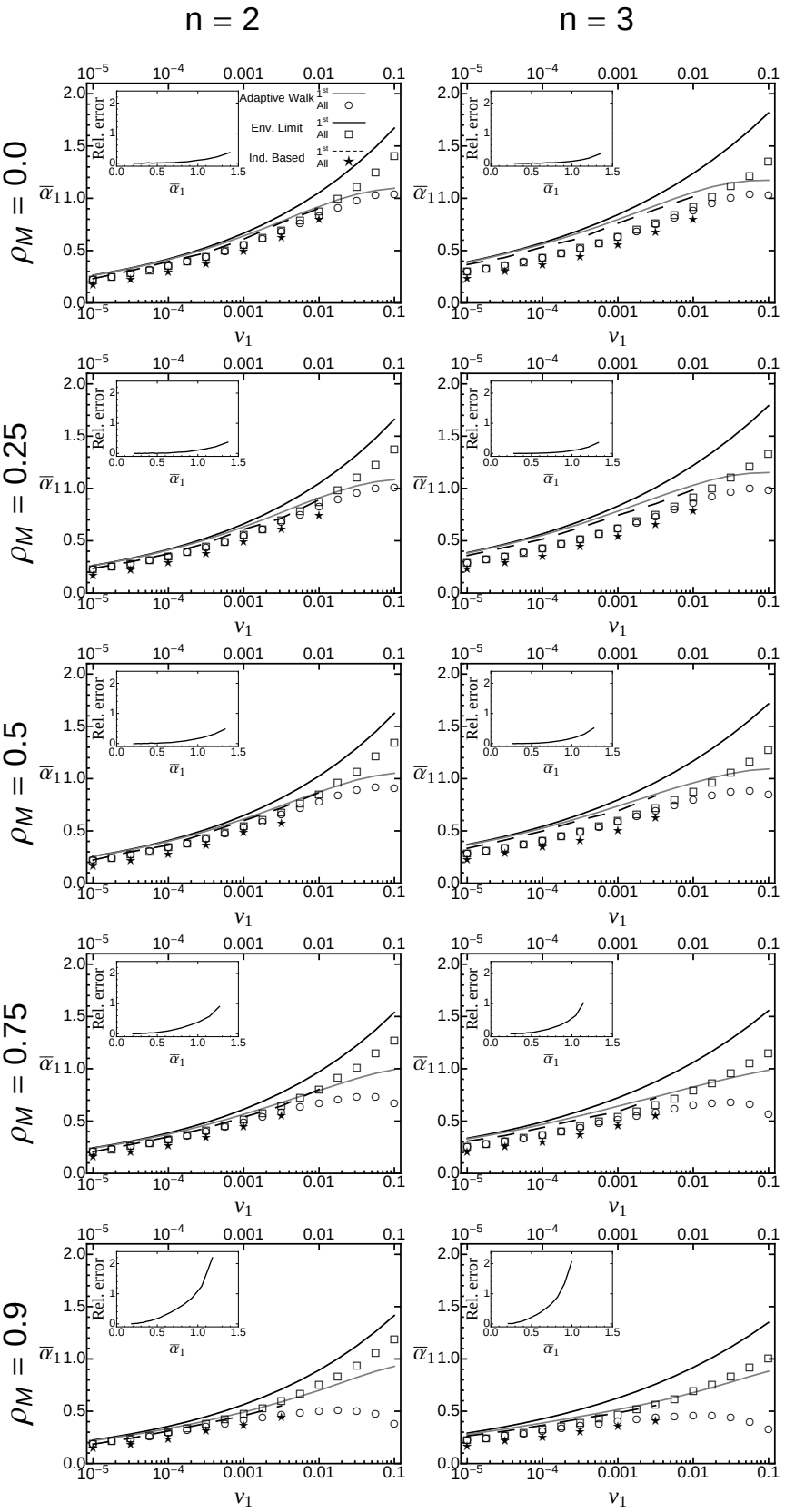

Figure S5_3 – Mean size $\bar{\alpha}_1$ of adaptive substitutions in the direction of the moving optimum, for the first step (lines) and over the entire adaptive walk (symbols), as a function of the rate of environmental change ν_1, for $n = 2$ and 3 traits and different values of mutational correlation ρ_M. "Adaptive walk" refers to adaptive-walk simulations with a normal distribution of new mutations, "Env. limit" to adaptive-walk simulations assuming a uniform distribution of new mutations (eq. S19), and "Ind. based" to individual-based simulations (with normally distributed new mutations). Also shown is the relative error over all steps incurred by "Env. limit" relative to "Adaptive walk". Parameters: $\Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0.0, m^2 = 1$.

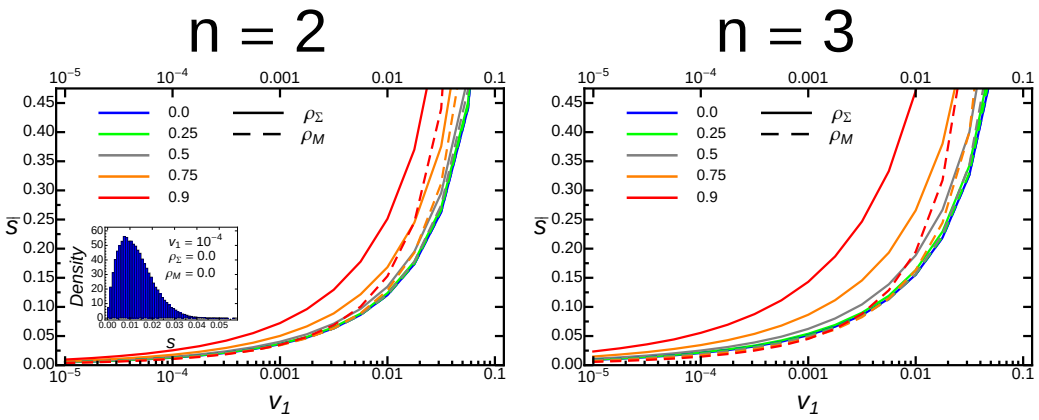

Figure S5_4 – Mean selection coefficient of adaptive substitutions as a function of the rate of environmental change for various strengths of mutational (dashed lines) and selectional (solid lines) correlations ρ_M and ρ_Σ. The inset gives a representative distribution of the selection coefficient for the isotropic case ($\rho_M = \rho_\Sigma = 0.0$) and $v_1 = 10^{-4}$. Note that with increasing v_1 the distribution becomes more asymmetric. Parameters: $\Theta = 1$.

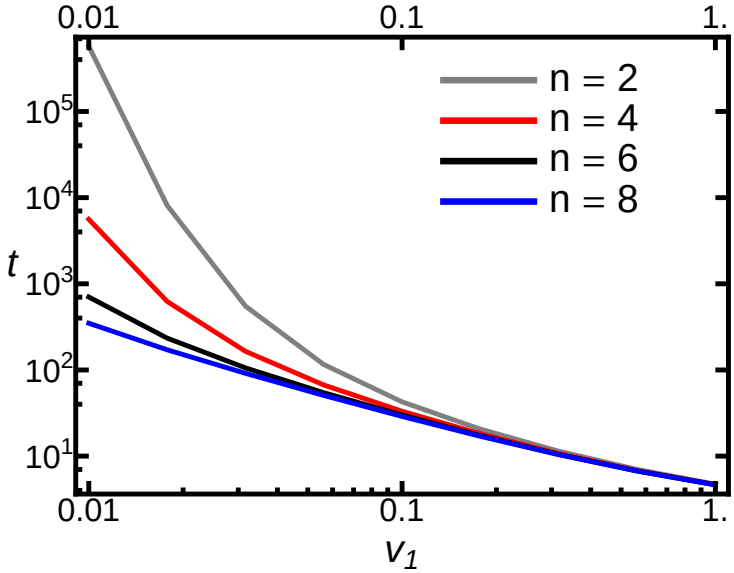

Figure S5_5 – The mean time to extinction for different levels of phenotypic complexity n as a function of the rate of environmental change. The mean extinction time was calculated based on 100, 000 adaptive-walk simulations, where populations were considered extinct when the mean fitness dropped below 0.5. Simulations that persisted for more than 1, 000, 000 generations were aborted for performance reasons. Parameter values are $\Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0.0, m^2 = 1$; the scaled rate of environmental change $\gamma = 10 \cdot v_1$.

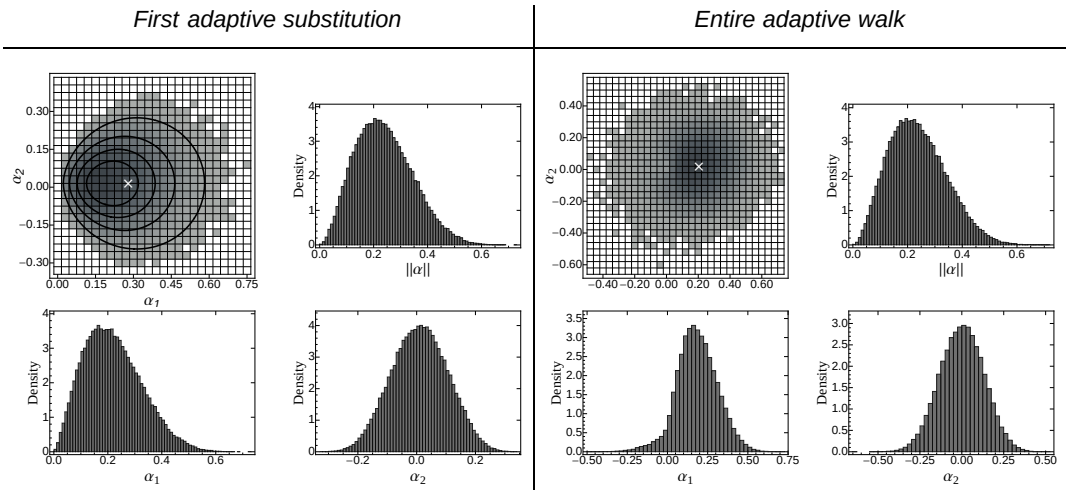

Figure S5_6 – The multivariate distribution of the first adaptive substitution (left) and over the entire adaptive walk (right) for $n = 2$ traits, when the optimum moves slowly in the direction of the first trait and the effects of new mutations are strongly correlated ($\rho_M = 0.9$). In the top-left figures on each side, shades of grey indicate the frequency of a given step size in adaptive-walk simulations with normally-distributed mutational effects (with dark grey corresponding to high frequency), with the white cross showing the observed mean. The contour lines on the left represent the probability density intervals predicted for a uniform distribution of new mutations (environmentally-limited regime, eq. S19; highest probability density intervals for $0.25, 0.5, 0.75, 0.95$ from inside out). Histograms show the marginal distribution of the first and second trait, α_1 and α_2, and the distribution of the total step size $||\boldsymbol{\alpha}||$. Parameter values are $v_1 = 10^{-5}, \Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0.0, m^2 = 1$; the scaled rate of environmental change $\gamma = 10^{-4}$.

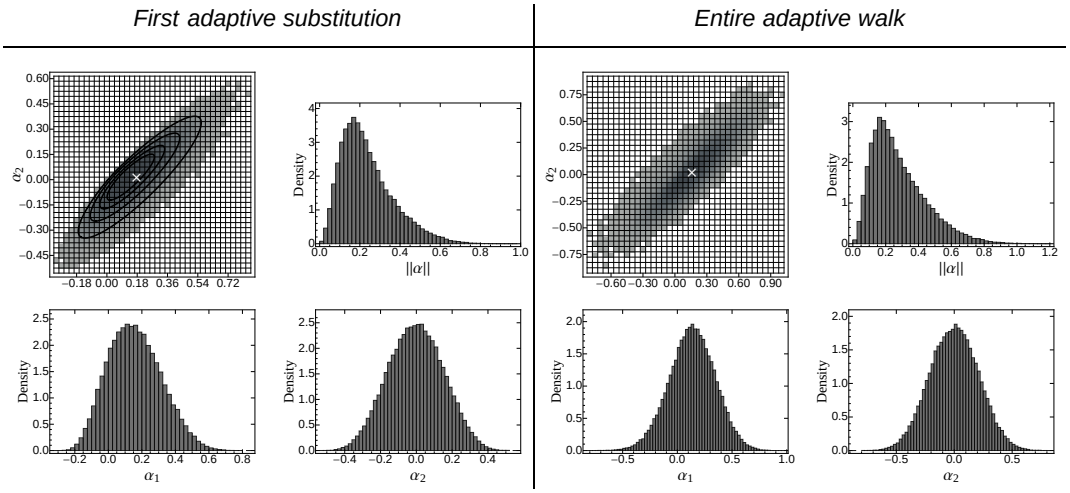

Figure S5_7 – The multivariate distribution of the first adaptive substitution (left) and over the entire adaptive walk (right) for $n = 2$ traits, when the optimum moves slowly in the direction of the first trait and selection is strongly correlated ($\rho_\Sigma = 0.9$). In the top-left figures on each side, shades of grey indicate the frequency of a given step size in adaptive-walk simulations with normally-distributed mutational effects (with dark grey corresponding to high frequency), with the white cross showing the observed mean. The contour lines on the left represent the probability density intervals predicted for a uniform distribution of new mutations (environmentally-limited regime, eq. S19; highest probability density intervals for $0.25, 0.5, 0.75, 0.95$ from inside out). Histograms show the marginal distribution of the first and second trait, α_1 and α_2, and the distribution of the total step size $||\boldsymbol{\alpha}||$. Parameter values are $v_1 = 10^{-5}, \Theta = 1, \sigma^2 = 10, m^2 = 1, \rho_M = 0$; the scaled rate of environmental change $\gamma = 10^{-4}$.

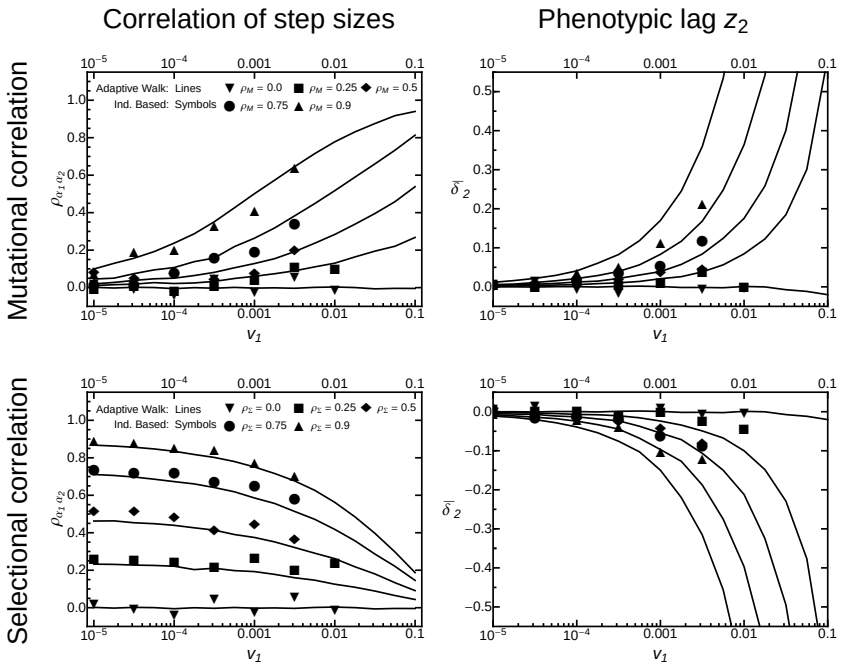

Figure S5_8 – The impact of mutational and selectional correlations on the distribution of adaptive substitutions for $n = 3$ traits. For details, see Fig. 5 of the main text.

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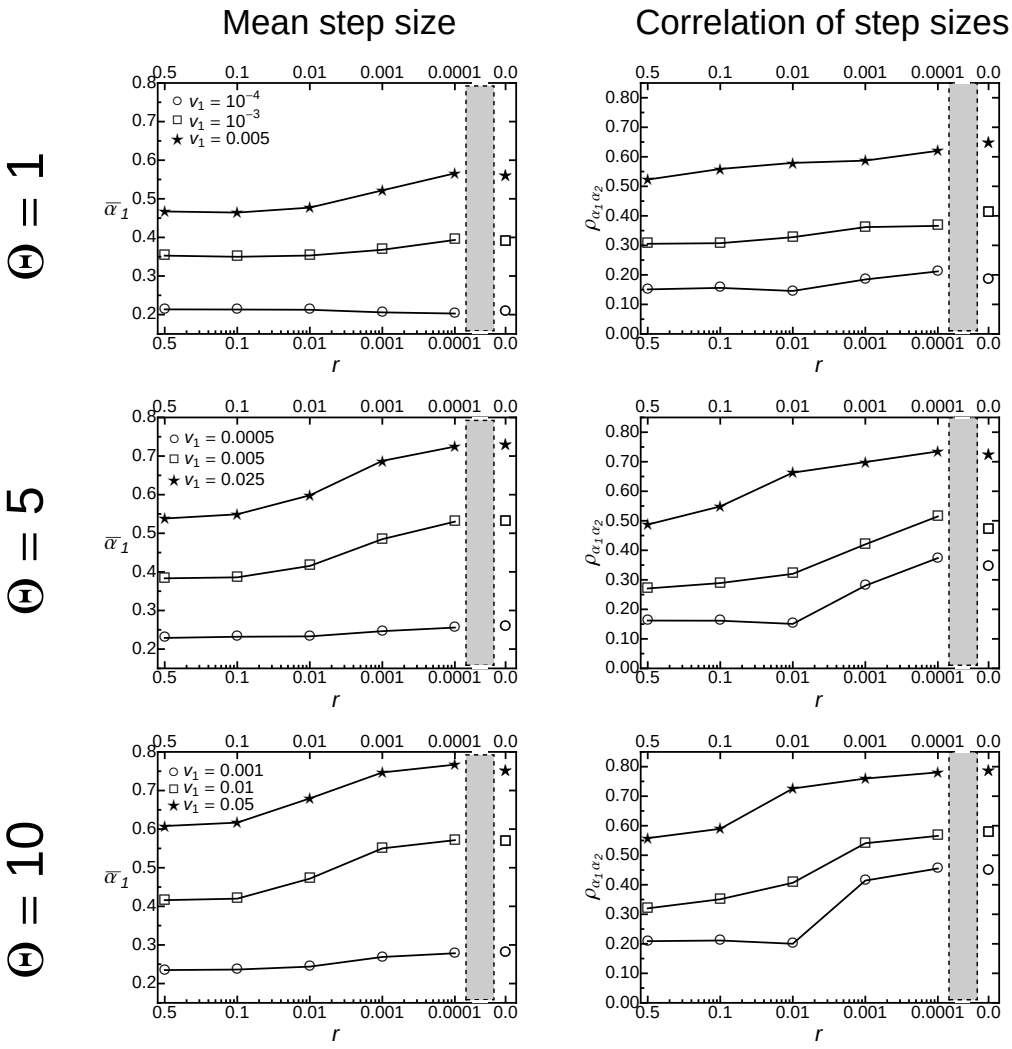

Figure S5_9 – The effects of linkage and interference between co-segregating alleles on the mean step size in direction of the moving optimum α_1 (left) and the correlation between adaptive substitutions ρ_{α_1,α_2} (right) under strong mutational correlations $\rho_M = 0.9$. The plots are based on 5000 replicated individual-based simulations. The population-wide mutation rate Θ was varied by increasing the per-locus mutation rate μ. Rates of environmental change v_1 were chosen such that the same three values of γ (i.e., the scaled rate of environmental change; see above; $\gamma(\circ) = 0.0035, \gamma(\square) = 0.035, \gamma(\bigstar) = 0.17$) applied for each Θ. Other parameters: $K = 1000, L = 10, \sigma^2 = 10, \rho_\Sigma = 0.0, m^2 = 1$.

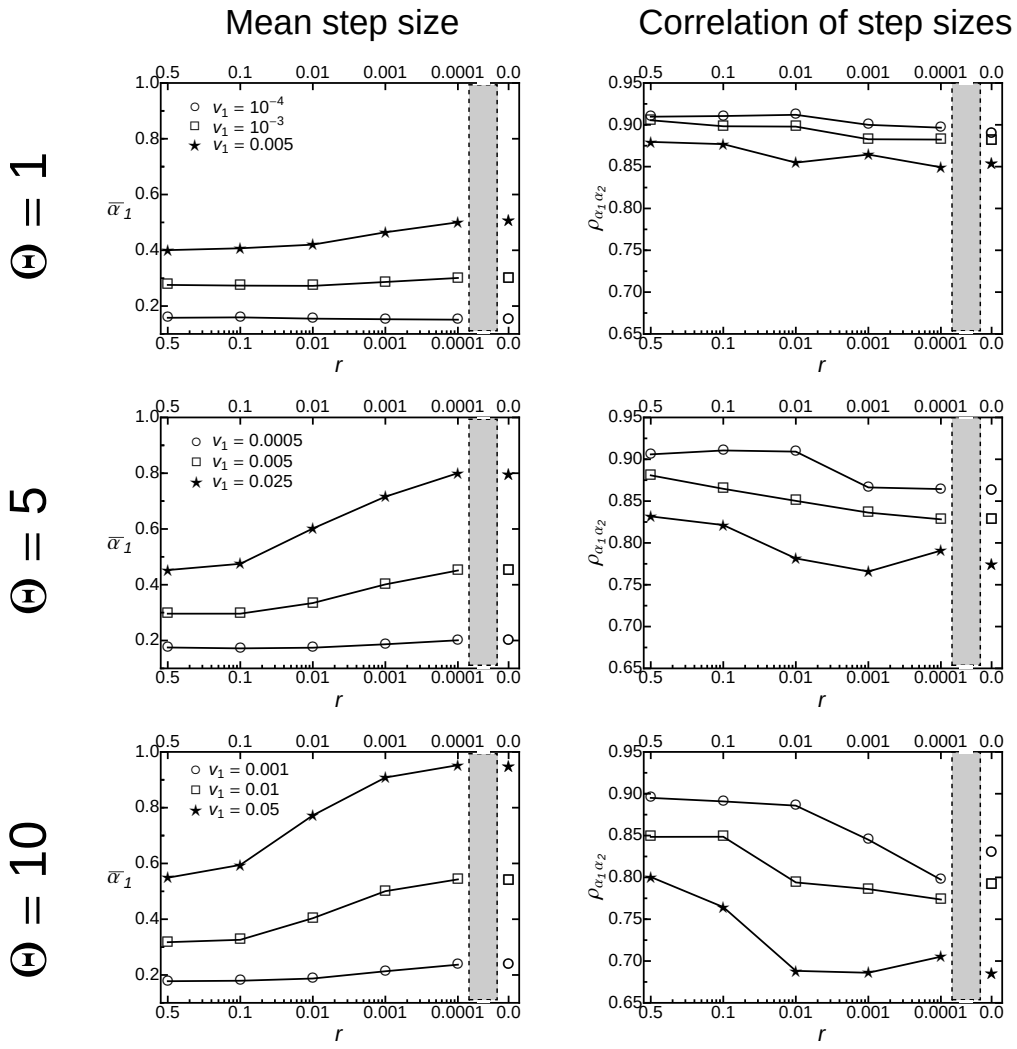

Figure S5_10 – The effects of linkage and interference between co-segregating alleles on the mean step size in direction of the moving optimum α_1 (left) and the correlation between adaptive substitutions ρ_{α_1,α_2} (right) under strong selectional correlations $\rho_\Sigma = 0.9$. The plots are based on 5000 replicated individual-based simulations. The population-wide mutation rate Θ was varied by increasing the per-locus mutation rate μ. Rates of environmental change v_1 were chosen such that the same three values of γ (i.e., the scaled rate of environmental change; $\gamma(\circ) = 0.00066, \gamma(\square) = 0.0066, \gamma(\bigstar) = 0.033$) applied for each Θ. Other parameters: $K = 1000, L = 10, \sigma^2 = 10, m^2 = 1, \rho_M = 0.0$.

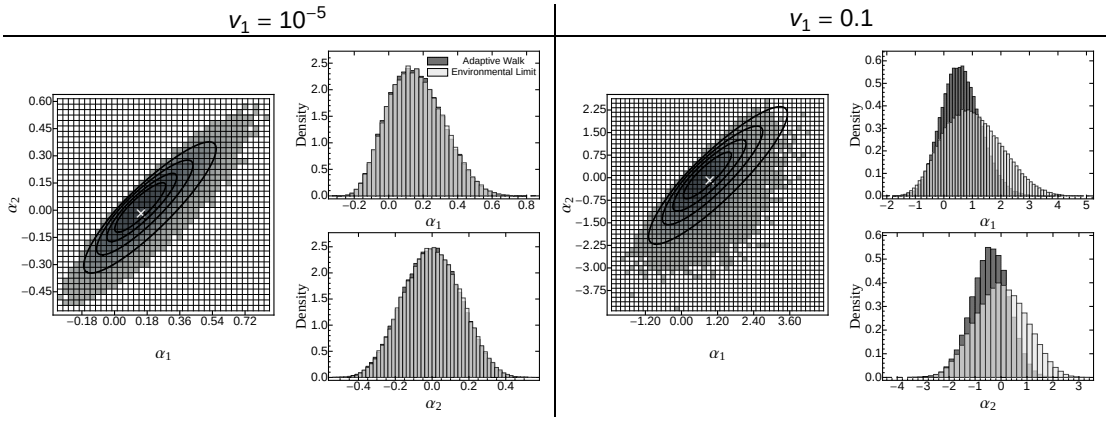

Figure S5_11 – The multivariate distribution of the first adaptive substitution in adaptive-walk simulations with strong selectional correlation ($\rho_\Sigma = 0.9$), illustrating the "diving-kite effect" (the negative bias in the α_2-direction) present for fast ($v_1 = 0.1$) but not for slow ($v_1 = 10^{-5}$) environmental change. The left-hand plot on each side is as in Figure S5_7, with shades of grey illustrating the distribution in adaptive-walk simulations with normally-distributed new mutations, and contour lines showing the prediction for a uniform distribution of new mutations (environmentally-limited regime, eq. S19). The histograms compare the marginal distributions of both traits for the two distributions of new mutations. Other parameters are identical to those in Figure S5_7.

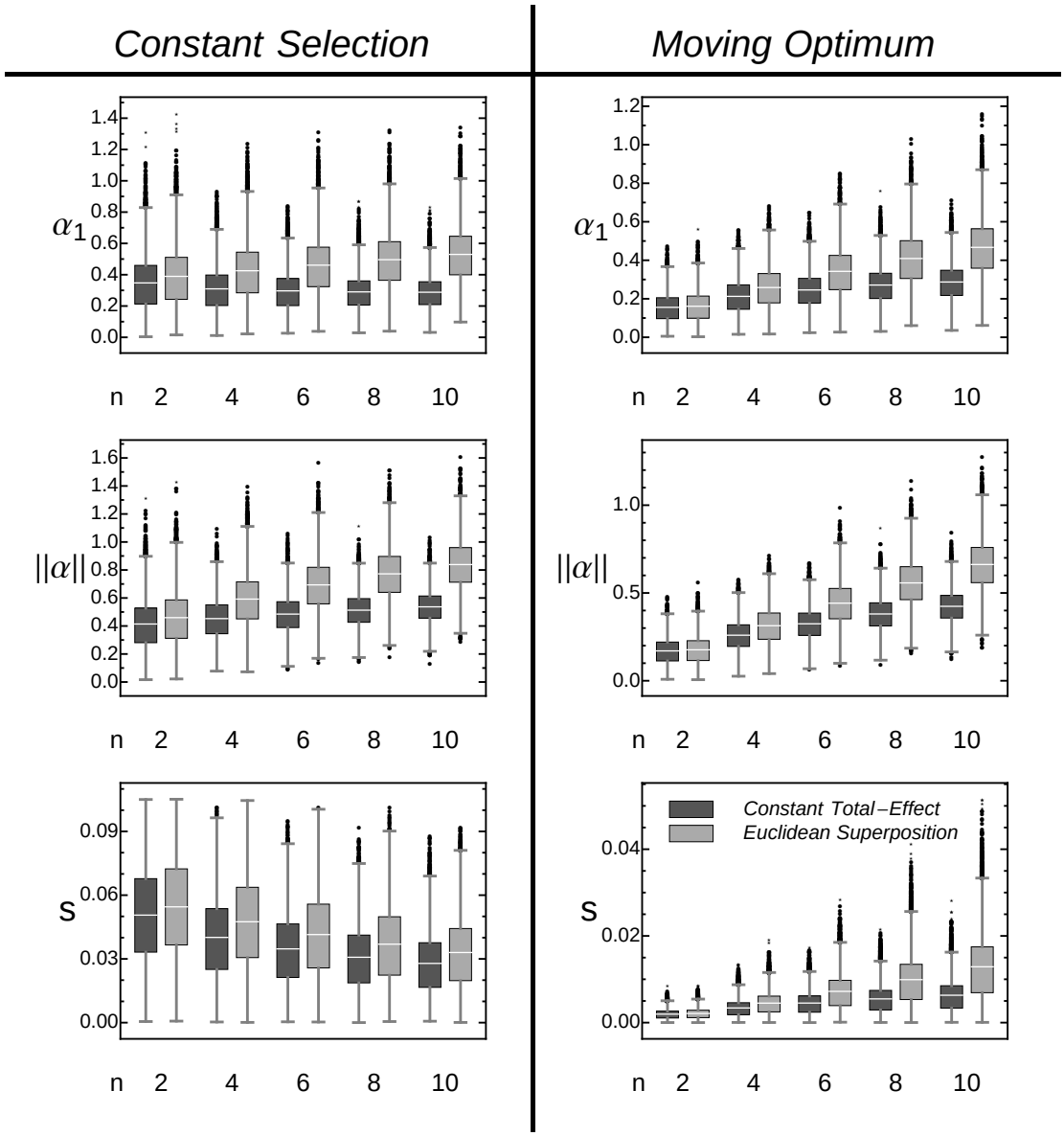

Figure S5_12 – Comparison of the first adaptive substitution under the constant total-effect (darker grey) and the Euclidean superposition model (lighter grey) for Fisher's geometric model with constant selection (left) and a moving optimum (right). The boxplots are based on 10000 replicated adaptive-walk simulations and show the distribution of step sizes in direction of the optimum α_1 (top row), the distribution of total step sizes $||\boldsymbol{\alpha}||$ and the distribution of the selection coefficient s of adaptive substitutions. Whiskers extend to maximally 1.5 times the size of the box. Horizontal white bars indicate the mean. In the constant selection case, the population started at an initial distance of 1 from the optimum. In the moving-optimum model, the rate of environmental change was $v_1 = 10^{-5}$. The variance of mutational effects was $m^2 = 0.1$ in the Euclidean superposition model and $0.1/\left(\sqrt{2}(\Gamma\left[(n+1)/2\right]/\Gamma\left[n/2\right])\right)$ in the constant total-effect model (here, the denominator is the expected mean of the norm of a multinormal distribution with covariance matrix $\mathbf{I}$, which is equal to the expectation of a χ-distribution with n degrees of freedom). Note that the constant total-effects model used here differs from the one in Orr (2000), because Orr only considered mutations of a single fixed total effect $||\boldsymbol{\alpha}||$ (i.e., his mutations are drawn from the surface of a hypersphere, whereas ours are drawn from a multivariate normal distribution). Other parameters: $\Theta = 1, \sigma^2 = 10, \rho_\Sigma = 0.0, \rho_M = 0.0$.

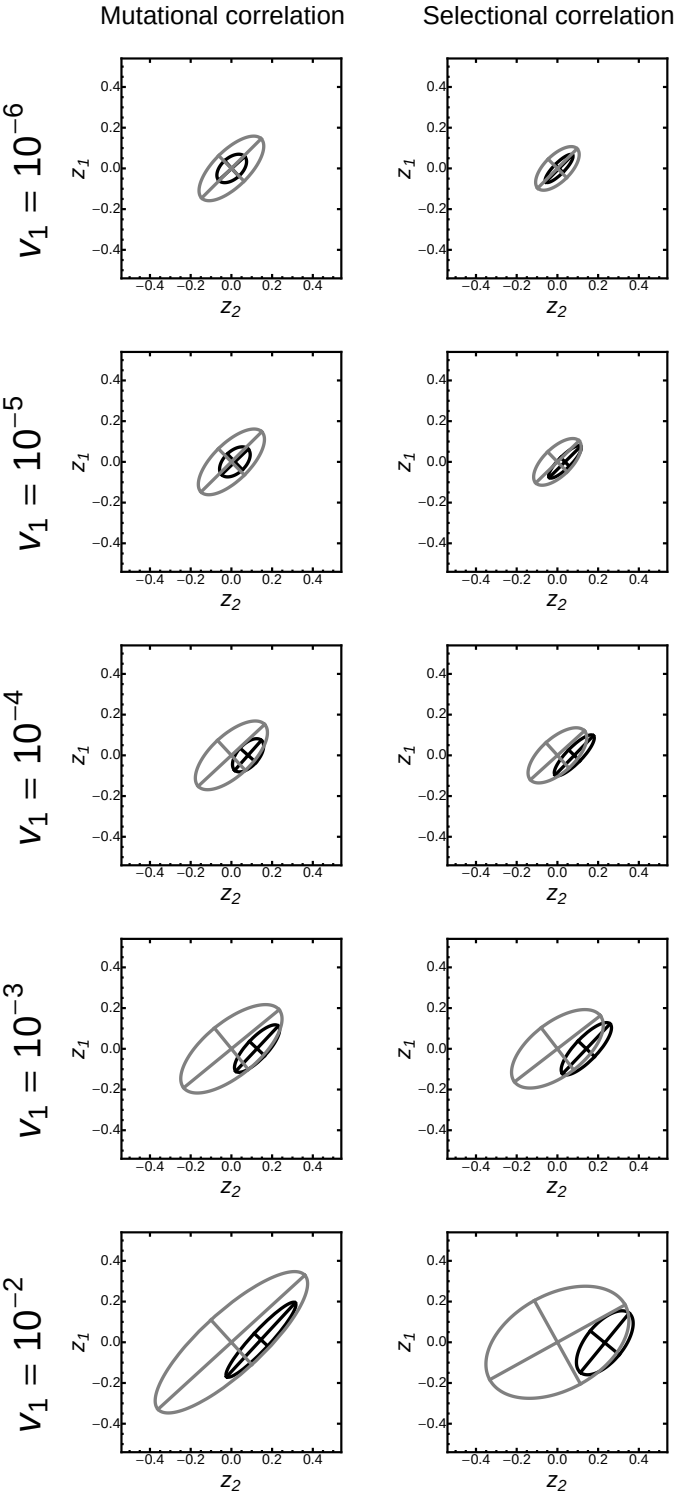

Figure S5_13 – The **G** matrix (grey ellipse) and the 90%-confidence ellipse of the distribution of adaptive substitutions (dark ellipse) under strong mutational ($\rho_M = 0.9$) and selectional ($\rho_\Sigma = 0.9$) correlation, for various rates of environmental change (v_1). Results are shown for individual-based simulations of 1000 adaptive substitutions. **G** was calculated as an average over samples taken every 100^{th} generation. Note that **G** increases with v_1. Parameters: $K = 1000$, $L = 50$, $\mu = 5 \times 10^{-5}$, $\sigma^2 = 10$, $m^2 = 0.05$.

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Information about submission and S. Matuszewski's contribution

STATUS:	published
JOURNAL:	Evolution 68(9): 2571–2588
DATE OF ACCEPTANCE:	15.05.2014

S. MATUSZEWSKI'S CONTRIBUTION: Contributed to the model design, derived the numerical and part of the analytical results, wrote simulation code and the manuscript draft.

Catch me if you can: On the importance of standing genetic variation for the genetics of adaptation in changing environments

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ABSTRACT. *Adaptation lies at the heart of Darwinian evolution. Accordingly, numerous studies have tried to provide a formal framework for the description of the adaptive process. Out of these two complementary modelling approaches have emerged: While so-called adaptive walk models typically consider adaptation from the successive fixation of* de-novo *mutations only, quantitative genetic models, on the other hand, assume that adaptation proceeds exclusively from preexisting standing genetic variation. The latter approach, however, has focussed on short-term evolution of population means and variances rather than on the statistical properties of adaptive substitutions. Our aim is to overcome what has been phrased "the most obvious theoretical limitation when describing the adaptive process" (Orr 2005b) and to describe the ecological and genetic factors that determine the genetic basis of adaptation from standing genetic variation. Specifically, we consider the evolution of a quantitative trait to gradually changing environment. By means of analytical approximations, we derive the distribution of standing adaptive substitutions, that is, the distribution of the phenotypic effects of those alleles that become fixed during adaptation and which originated from standing genetic variation. Our results are checked against individual-based simulations. We find that (i) compared to adaptation from* de-novo *mutations, adaptation from standing variation proceeds by the fixation of more alleles of small effect; (ii) in contrast to models that consider new mutations only, faster environmental change can enable the population to remain better adapted and to traverse larger distances in phenotype space when standing genetic variation is the sole source for adaptation.*

1. Introduction

One of the biggest surprises that has emerged from evolutionary research in the past few decades is that, in contrast to what has been claimed by the neutral theory (Kimura 1983), adaptive evolution at the molecular level is wide-spread. In fact, empirical studies concluded that about 45% of all amino acid changes between *Drosophila simulans* and *D. yakuba* are adaptive (Smith and Eyre-Walker 2002; Orr 2005b). Along the same line, Wichman et al. (1999) evolved the single-stranded DNA bacteriophage ΦX174 to high temperature and a novel host and found that 80 – 90% of the observed nucleotide substitutions had an adaptive effect. These and other results have led to an increased interest in providing a formal framework for the adaptive process, that goes beyond traditional

population- and quantitative genetic approaches, by considering the statistical properties of suites of substitutions of "individual mutations that have individual effects" (Orr 2005a). In general, selection following a change in the environmental conditions may either act on *de-novo* mutations, or on alleles already present in the population, also known as standing genetic variation. Consequently, from the numerous studies that have attempted to address this subject, two complementary modelling approaches have emerged.

So-called adaptive-walk models (Gillespie 1984; Kauffman and Levin 1987; Orr 2002, 2005b) typically assume that selection is strong compared to mutation, so that the population can be considered monomorphic all the time and all observed evolutionary change is the result of *de-novo* mutations. These models have produced several robust predictions (Orr 1998, 2000; Martin and Lenormand 2006), which are supported by growing empirical evidence (Cooper et al. 2007; Rockman 2012; Hietpas et al. 2013), and provided a statistical framework for the fundamental event during adaptation, that is, the substitution of a resident allele (i.e., gene variant) by a beneficial mutation. Specifically, the majority of models (Gillespie 1984; Orr 2000; Martin and Lenormand 2006) consider the effect-size distribution of adaptive substitutions following a sudden change in the environment. Recently, Kopp and Hermisson (2009b) and Matuszewski et al. (2014) shifted the focus to gradual environmental change.

In contrast, quantitative-genetic models consider an inexhaustible pool of preexisting standing genetic variants as the sole source for adaptation. Evolving traits are assumed to have a polygenic basis, where many loci contribute small individual effects, such that the distribution of trait values approximately follows a Gaussian distribution (Bulmer 1980; Barton and Turelli 1991; Kirkpatrick et al. 2002). Since the origins of quantitative genetics lie in the design of plant and animal breeding schemes (Wricke and Weber 1986; Tobin et al. 2006; Hallauer et al. 2010), the traditional focus of these models was on predicting short-term changes in the population mean phenotype (often assuming constant genetic variances and covariances), and not on the fate and effect of alleles at individual genetic loci. The same is true for the relatively small number of models that have studied the contribution of new mutations to the response of artificial selection (Hill and Rasbash 1986a) and the shape and stability of the **G**-matrix (i.e., the variance-covariance matrix of genotypes; Jones et al. 2004, 2012).

It is only in the past decade that population geneticist have thoroughly addressed adaptation from standing genetic variation at the level of individual substitutions (Orr and Betancourt 2001; Hermisson and Pennings 2005; Chevin and Hospital 2008). Hermisson and Pennings (2005) calculated the probability of adaptation from standing genetic

variation following a sudden change in the selection regime. They found that, for small-effect alleles, the fixation probability is considerably increased relative to that from new mutations. Similarly, Chevin and Hospital (2008) showed that the selective dynamics at a focal locus are substantially affected by genetic background variation. Performing experimental evolution in yeast, Lang et al. (2011) followed beneficial mutations in hundreds of populations and showed that the selective advantage of a mutation plays only a limited role in determining its ultimate fate. Instead, fixation or loss is largely determined by variation in the genetic background – which need not to be preexisting, but could quickly be generated by a large number of new mutations. Still, predictions for the genetics of adaptation from standing genetic variation have been verbal at best, stating that "compared with new mutations, adaptation from standing genetic variation is likely to lead to faster evolution [and] the fixation of more alleles of small effect [...]" (Barrett and Schluter 2008). Thus, despite recent progress, one of the central questions still remains unanswered: From the multitude of standing genetic variants segregating in a population, which are the ones that ultimately become fixed and contribute to adaptation, and how does their distribution differ from that of *de-novo* mutations?

The aim of the present article is to contribute to overcoming what has been described as "the most obvious theoretical limitation when describing the adaptive process" (Orr 2005b) and to study the ecological and genetic factors that determine the genetic basis of adaptation from standing genetic variation. Specifically, we consider the evolution of a quantitative trait in a gradually changing environment. We develop an analytical framework that accurately describes the distribution of standing adaptive substitutions and discuss its dependence on the effective population size, the strength of selection and ecological factors.

In line with Barrett and Schluter (2008), we find that, compared to new mutations, adaptation from standing genetic variation proceeds, on average, by smaller steps. Our analysis shows that the genetic basis of adaptation from standing genetic variation crucially depends on the efficacy of selection as defined by the population size, the strength of (stabilizing) selection and the tempo of environmental change. In contrast to studies that consider adaptation from new mutations only (Perron et al. 2008; Bell and Gonzalez 2011; Lindsey et al. 2013; Bell 2013), we find that, when standing genetic variation is the sole source for adaptation, faster environmental change can enable the population to remain better adapted and to traverse larger distances in phenotype space.

2. Model and Methods

2.1. Phenotype, Selection and Mutation

We consider the evolution of a diploid population of N individuals with discrete and non-overlapping generations characterized by a single phenotypic trait z, which is under Gaussian stabilizing selection with regard to a time-dependent optimum $z_{\text{opt}}(t)$:

$$w(z,t) = \exp\left[-\frac{\left(z - z_{\text{opt}}(t)\right)^2}{2\sigma_s^2}\right], \tag{1}$$

where σ_s^2 describes the width of the fitness landscape. Throughout this paper we choose the linearly moving optimum,

$$z_{\text{opt}}(t) = vt, \tag{2}$$

where v is the rate of environmental change.

Mutations enter the population at rate Θ and we assume that their phenotypic effect size α follows a Gaussian distribution with mean 0 and variance σ_m^2 (which we will refer to as the distribution of new mutations), that is

$$p(\alpha) = \frac{1}{\sqrt{2\pi\sigma_m}} \exp\left(-\frac{\alpha^2}{2\sigma_m^2}\right). \tag{3}$$

Throughout this paper we equate genotypic with phenotypic values and, thus, neglect any environmental variance. Note that this model is, so far, identical to the moving-optimum model proposed by Kopp and Hermisson (2009b) (see also Bürger 2000).

Based on this general formulation, we derive two complementary submodels that make additional assumptions on the genetic architecture (single- vs. multi-locus framework), the mutational process (recurrent mutation vs. infinite sites model) and population dynamics (present vs. absent). More details are given in subsection 2.3.1 Wright-Fisher simulations and 2.3.2 Individual-based simulations, respectively.

2.2. Theoretical Background

In the following, we briefly recapitulate results from previous studies that form the basis for our analytical derivations. A summary of our notation is given in Table 1.

2.2.1. The probability for adaptation from standing genetic variation for a single bi-allelic locus after a sudden environmental change

Hermisson and Pennings (2005) studied the situation where selection at a single bi-allelic locus changes following a sudden environmental shift. In particular, they derived the probability for a mutant allele—which was neutral or deleterious prior to the change but has become beneficial in the new environment—to reach fixation. In the continuum limit for allele frequencies x this probably is given by

$$P_{\mathrm{SGV}} = \int_0^1 \rho(x)\Pi_x \mathrm{d}x, \tag{4}$$

where $\rho(x)$ is the density function for the allele frequency of the mutant allele in mutation-selection-drift balance and Π_x denotes its fixation probability.

For a mutant allele present at frequency x and with selective advantage s_b in the new environment, the fixation probability is given by (Kimura 1957)

$$\Pi_x(s_b) \approx \frac{1 - \exp[-4N_e s_b x]}{1 - \exp[-4N_e s_b]}. \tag{5}$$

There are two points to make here. First, mutational effects in the Hermisson and Pennings (2005) model are directly proportional to fitness, whereas mutations in our model affect a phenotype under selection. Second, s_b, in our framework, denotes the (beneficial) selection coefficient for heterozygotes.

Approximations for $\rho(x)$ can be obtained using standard diffusion theory (e.g., Ewens 2004). If the mutant allele was neutral prior to the change in the selection scheme

$$\rho(x) = C x^{\Theta-1} \frac{1 - x^{1-\Theta}}{x - 1}. \tag{6}$$

Here, $C = (\gamma + \psi(\Theta))^{-1}$ denotes a normalization constant where $\gamma \approx 0.577$ is Euler's gamma and $\psi(\bullet)$ is the polygamma function.

Similarly, if the mutant allele was deleterious before the environmental change (with negative selection coefficient s_d) the allele-frequency distribution is given by

$$\rho(x) = C \frac{\left(1 - \exp\left[(1-x)4N_e s_d\right]\right) x^{\Theta-1}}{x - 1} \mathrm{d}x, \tag{7}$$

where $C = ({}_1F_1(0, \Theta, 4N_e s_d))^{-1}$ denotes a normalization constant and ${}_1F_1(a, b, c)$ is the hypergeometric function.

If the allele was sufficiently deleterious ($4N_e|s_d| \geq 10$), equation (7) can further be approximated as

$$\rho(x) = Cx^{\Theta-1} \exp[-4N_e|s_d|x], \tag{8}$$

where $C = (\frac{\gamma[\Theta, 4N_e|s_d|]}{(4N_e|s_d|)^{\Theta}})^{-1}$ again denotes a normalization constant with $\gamma[a, b] = \int_0^b t^{a-1} \exp[-t]\mathrm{d}t$ denoting the lower incomplete gamma function.

Finally, the probability that a population successfully adapts from standing genetic variation can be derived as

$$\begin{aligned} P_{\mathrm{SGV}} &= 1 - \left(1 + \frac{4N_e s_b}{4N_e|s_d|+1}\right)^{-\Theta} \\ 1- &\approx \exp\left[-\Theta \log\left[\frac{4N_e s_b}{4N_e|s_d|+1}\right]\right]. \end{aligned} \tag{9}$$

2.2.2. Fixation probabilities under time-inhomogeneous selection

In gradually changing environments, the selection coefficient of a given (mutant) allele is not fixed but changes over time (i.e., as the position of the optimum changes). Uecker and Hermisson (2011) recently developed a mathematical framework based on branching-process theory to describe the fixation process of a beneficial allele under temporal variation in population size and/or selection pressures. They showed that the probability of fixation for a mutation starting with n initial copies is given by

$$\Pi_{\mathrm{fix}}(n) = 1 - \left(1 - \frac{1}{\varphi}\right)^n, \tag{10a}$$

where

$$\frac{1}{\varphi} = \frac{2}{1 + \int_0^{\infty} (N(0)/N_e(t)) \exp\left[-\int_0^t s(\tau) d\tau\right] \mathrm{d}t}. \tag{10b}$$

Assuming that the population size remains constant and that the selection coefficient increases linearly in time, $s(t) = s_d + s_t t$, equation (10a) becomes

$$\Pi_{\mathrm{fix}} = 1 - \left(1 - \left[1 + \xi \sqrt{\frac{\pi}{2s_t}} \exp\left(\frac{s_d^2}{2s_t}\right) \mathrm{erfc}\left(\frac{s_d}{\sqrt{2s_t}}\right)\right]^{-1}\right)^n, \tag{11}$$

where erfc(•) denotes the Gaussian error function and ξ is a scaling constant.

2.2.3. Evolution of a focal locus in the presence of genetic background variation

Both the Hermisson and Pennings (2005) and the Uecker and Hermisson (2011) framework study evolution at a single locus only. In the quantitative-genetics view of adaptation, however, there is simultaneous selection at many loci that contribute to an adaptive trait. Assuming that the genetic values (of individuals) for that trait follow a Gaussian distribution with genetic variance σ_g^2, the change in the mean phenotype is given by

$$\Delta\bar{z} = \sigma_g^2\beta, \tag{12a}$$

where

$$\beta = \frac{\partial \log(\bar{w})}{\partial \bar{z}} \tag{12b}$$

denotes the selection gradient, which measures the proportional change in log mean fitness per unit change of the mean phenotype (Lande 1976).

When individual alleles influencing the same trait segregate in the standing genetic variation, the selective dynamics of any individual allele and therefore its fate are critically affected by the collective evolutionary response at other loci, due to interference effects (epistasis for fitness). In particular, any allele that brings the mean phenotype closer to the optimum simultaneously decreases the selective advantage of other such alleles. Thus, if evolution of the genetic background allows the population to closely follow the optimum, the large-effect alleles at any given locus are likely to remain deleterious (as their carriers would overshoot the optimum). Therefore, the probability for alleles from the standing genetic variation to reach fixation crucially depends on the genetic background, which determines their time-dependent selection coefficient.

This issue was first addressed by Lande (1983), who proposed a model that considers the simultaneous evolution at a focal locus and of genetic background variation that both affect a quantitative trait evolving towards a constant optimum. Adapting this approach, Chevin and Hospital (2008) analyzed the effect of genetic background variation on the allele trajectory of a focal allele sweeping to fixation, and Gomulkiewicz et al. (2010) studied the probability of adaptation to novel environments. In essence, all studies stressed the fact that genetic background variation cannot be neglected and critically affects the adaptive outcome. To assess the probability of adaptation from standing genetic variation for individual mutant alleles, while accounting for simultaneous evolution at other

loci, we introduce a genetic background z_B (evolving according to equation 12) into the Hermisson and Pennings (2005) and Uecker and Hermisson (2011) frameworks.

2.3. Simulations

To check our analytical approximations, we used two complementary simulation approaches, which are explained in detail in the subsequent paragraphs. Both programs were written in C++ and make use of the Gnu Scientific Library (Galassi et al. 2009). Mathematica (Wolfram Research, Inc., Champaign, USA) was used for the numerical evaluation of integrals and to create plots and graphics, making use of the LevelScheme package (Caprio 2005).

2.3.1. Wright-Fisher simulations

Following Hermisson and Pennings (2005), we implemented a multinomial Wright-Fisher (WF) sampling approach (available upon request). While this framework allows the adaptive process to be simulated fast and efficiently, it can only serve as an approximation since it does not include population dynamics nor does it have an explicit genetic context (see below).

Genome. Instead of following allele trajectories across multiple loci, we focus on the effect of selection on a focal locus affecting the quantitative trait of interest and on genetic background variation for this trait, which summarizes the collective evolutionary response by other loci. Thus, this model effectively reduces to a single-locus framework, where the focal locus is assumed to be in linkage equilibrium with the genetic background (i.e., with all other loci). For a fixed allelic effect α, mutations appear recurrently at rate Θ at the focal locus, where they convert ancestral alleles into derived standing and derived *de-novo* alleles, depending on whether they appeared prior to or after the environmental change. Accordingly, despite of a normally distributed genetic background, there are at most three types of (focal) alleles in the population, where each type only "feels" the mean background $\bar{z}_B$, which evolves according to equation (12) with constant σ_g^2. Note that dynamics at the focal locus are coupled with the genetic background (and *vice versa*), meaning that the evolutionary responses at the focal locus and the genetic background are interdependent. Furthermore, the amount of genetic background variation σ_g^2 in this model serves as a free parameter that is independent of Θ, N_e and σ_s^2.

Procedure. We follow the evolution of $2N_e$ haploid individuals in the presence of genetic background variation σ_g^2 in a gradually changing environment. Each generation is generated by binomial or multinomial sampling, where the probability of choosing an allele of a given type (wild-type, derived standing, derived *de-novo*) is weighted by its respective fitness. Furthermore, $\bar{z}_B$ evolves deterministically according to equation (12) with constant σ_g^2. To let the population reach mutation-selection-drift equilibrium each simulation is started $4N_e$ generations before the environment starts changing. Initially, the population consists of only ancestral alleles "0"; the derived allele "1" is created by mutation. If the derived allele reaches fixation by drift, it is itself denoted "ancestral"; i.e., the population is set back to the initial state. After $4N_e$ generations, the selection coefficient of the derived allele increases from neutral or deleterious (i.e., $s_d \leq 0$) until it may eventually become beneficial (i.e., $s_b(t) > 0$). Mutations now convert ancestral alleles into new derived alleles (using a different symbol, "2") with the same selective advantage $s_b(t)$. New mutational input is stopped $M = 0.1N_e$ generations after the environmental change (for details see Hermisson and Pennings 2005). Simulations continue until the ancestral allele either fixes or gets lost. Each run has four possible outcomes: Fixation of 0, 1, or 2 or of 1 and 2 together. In the following, fixation of "1" or "1 and 2" will both be considered as adaptation from standing genetic variation. Fixation probabilities are estimated from 100,000 runs.

2.3.2. Individual-based simulations

We conducted individual-based simulations (IBS; available upon request; see Bürger 2000; Kopp and Hermisson 2009b) to explicitly model the simultaneous evolution at multiple loci, while making additional assumptions about the genetic architecture of the selected trait, the life cycle of individuals and the regulation of population size.

Genome. Individuals are characterized by a linear (continuous) genome of diploid loci, which additively determine the phenotype z (i.e., there is no phenotypic epistasis; note that there is, however, epistasis for fitness).

We do not fix the number of loci a-priori, but instead assume that every mutation occurring at constant rate u per haplotype creates a unique polymorphic locus on the genome, whose position is drawn randomly from a uniform distribution on the unit interval. Thus, each locus only consists of a neutral wild-type and a mutant allele with phenotypic effect α. Thus, we effectively design a bi-allelic infinite-sites model, where allelic effects are drawn from a continuum (eq. 3).

To monitor adaptive substitutions, we introduce a population-consensus genome $\mathcal{G}$ that keeps track of all loci (i.e., all mutant alleles) that are segregating in the population. Mutant alleles that have become fixed in the population (i.e., that have risen to frequency of one) are declared the new wild-type allele and their phenotypic effect is reset to 0. The phenotypic effects of all fixed mutations are taken into account by a variable z_{fix}, which can be interpreted as a phenotypic baseline effect. Thus, the phenotype z of an individual i is given by

$$z_i = z_{\text{fix}} + \sum_{h\in\{1,2\}} \sum_{l\in\mathcal{G}} \mathbb{1}(i,l,h)\alpha_l.$$

where

$$\mathbb{1}(i,l,h) = \begin{cases} 1 & \text{if individual } i \text{ carries mutant allele } \alpha \text{ at locus } l \text{ on haplotype } h \\ 0 & \text{otherwise.} \end{cases}$$

Life cycle. Each generation, the following steps are performed:

(1) *Viability selection:* Individuals are removed with probability $1-w(z)$ (see eq. 1).

(2) *Population regulation:* If, after selection, the population size N exceeds the carrying capacity K, $N - K$ randomly chosen individuals are removed.

(3) *Reproduction:* The surviving individuals are randomly assigned to mating pairs, and each mating pair produces exactly B offspring (typically, $B = 4$). The offspring genotypes are derived from the parent genotypes by taking into account segregation, recombination and mutation.

Recombination. We assume that recombination is free, that is, all loci are unlinked, so that the number of crossing-over events tends to infinity. For each locus on the maternal and/or paternal haplotype a Bernoulli distributed random number is drawn to determine whether the offspring haplotype will receive the maternal or the paternal allele at that locus.

Simulation initialization and termination. Starting from a population of K genetically identical and homozygous individuals with phenotype $z = 0$ (i.e., the population was perfectly adapted at $t = 0$), we allowed for the establishment of genetic variation by letting the population evolve for 10,000 generations under stabilizing selection with a

constant optimum. Increasing the number of generations had no effect on σ_g^2. Following this equilibration time, the optimum started moving, and simulations were stopped once all alleles from the standing genetic variation had either been fixed or lost (i.e., when $\sigma_g^2 = 0$), and replicated until a total number of 5000 standing adaptive substitutions was recorded.

Table 1 – A summary of notation and definitions.

α	phenotypic effect of mutation
$p(\alpha)$	(Gaussian) distribution of new mutations
z	phenotype
$\bar{z}_{\mathrm{B}}$	mean genetic background phenotype
v	rate of environmental change
$w(z, z_{opt}(t))$	(Gaussian) fitness function
σ_s^2	width of Gaussian fitness function
σ_m^2	variance of new mutations
σ_g^2	genetic variance
$s(\alpha, t)$	time-dependent selection coefficient for allele with phenotypic effect α
s_d	(deleterious) selection coefficient prior to environmental change
s_b	(beneficial) selection coefficient after environmental change
s_t	rate of selection coefficient increase
x	frequency of mutant allele
N_e	effective population size
Θ	population-wide mutation rate
Π_{fix}	fixation probability
$\rho(x, \alpha)$	Distribution of mutant allele frequency x at a single locus with phenotypic effect α
P_{SGV}	Probability to adapt from standing genetic variation
p_{SGV}	Distribution of standing substitutions

3. Results

In the following we calculate the probability that alleles from the standing genetic variation become fixed when adapting to a moving phenotypic optimum, and we derive their effect-size distribution. Note that the former will be calculated under the assumption of recurrent mutation (see 2.3.1 Wright-Fisher simulations), whereas the later is derived under an infinite-sites model (see 2.3.2 Individual-based simulations).

3.1. The probability for adaptation from standing genetic variation

The selection coefficient at time t of a focal mutant allele with effect α can be calculated as

$$\begin{aligned} s(\alpha, t) &= \frac{w(\alpha + \bar{z}_{\mathrm{B}}(t), t)}{w(\bar{z}_{\mathrm{B}}(t), t)} - 1 \\ &\approx -\frac{\alpha^2}{2\left(\sigma_s^2 + \sigma_g^2\right)} + \frac{\alpha}{\sigma_s^2 + \sigma_g^2}(vt - \bar{z}_{\mathrm{B}}(t)). \end{aligned} \tag{14}$$

Note that the width of the fitness landscape is somehow "stretched" by the genetic background variance σ_g^2. Assuming that the distribution of phenotypic values from the genetic background is Gaussian and the genetic variance remains constant,

$$\bar{z}_{\mathrm{B}}(t) \approx vt - \frac{v}{\gamma}(1 - (1 - \gamma)^t) \tag{15a}$$

with

$$\gamma = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_s^2} \tag{15b}$$

(Bürger and Lynch 1995). Note that the amount of standing genetic variation in our individual-based simulations (subsection 2.3.2) is accurately predicted by the Stochastic-House-Of-Cards (SHC) approximation (not shown; Bürger and Lynch 1995)

$$\sigma_g^2 = \frac{\Theta\sigma_m^2}{1 + \frac{N_e\sigma_m^2}{\sigma_s^2}}. \tag{16}$$

The reason is that, with an infinite-sites model, there is no recurrent mutation and thus no intra-locus competition between co-segregating alleles that could reduce the amount of genetic variation (e.g., Alvarez-Castro et al. 2009).

Plugging into equation (14) then yields the selection coefficient,

$$s(\alpha, t) \approx -\frac{\alpha^2}{2\left(\sigma_s^2 + \sigma_g^2\right)} + \frac{\alpha v}{\gamma\left(\sigma_s^2 + \sigma_g^2\right)}(1 - (1 - \gamma)^t). \tag{17}$$

Assuming that the population is perfectly adapted at $t = 0$ ($\bar{z}_B = 0$), the (deleterious) selection coefficient is given by

$$s(\alpha, 0) = -\frac{\alpha^2}{2\left(\sigma_s^2 + \sigma_g^2\right)}.$$

Unlike in the model without genetic background variation (Kopp and Hermisson 2009b), $s(\alpha, t)$ does not increase linearly, but instead depends on the evolution of the phenotypic lag between the optimum and the mean background phenotype. In particular, if v is less than or equal to the critical rate of environmental change for population persistence (Bürger and Lynch 1995), the population will reach a dynamic equilibrium with $\Delta\bar{z} = v$, where it follows the optimum with a constant lag $\delta_{\text{eq}} = \frac{v}{\gamma}$ (Bürger and Lynch 1995). Consequently, the selection coefficient approaches

$$\lim_{t\to\infty} s(\alpha, t) = -\frac{\alpha^2}{2\left(\sigma_s^2 + \sigma_g^2\right)} + \frac{\alpha v}{\gamma\left(\sigma_s^2 + \sigma_g^2\right)}. \tag{18}$$

In this case, the largest obtainable selection coefficient is at $\alpha = \frac{v}{\gamma}$ (i.e., $\alpha = \delta_{\text{eq}}$) and evaluates to

$$s_{\max} = s(\frac{v}{\gamma}, \infty) = \frac{v^2}{2\gamma^2\left(\sigma_s^2 + \sigma_g^2\right)}. \tag{19}$$

The range of allelic effects α which can reach a positive selection coefficient is bounded by $\alpha_{\min} = 0$ and $\alpha_{\max} = 2\frac{v}{\gamma}$ (i.e., twice the equilibrium lag). Note that in previous adaptive-walk models (e.q., Kopp and Hermisson 2009b; Matuszewski et al. 2014) there was no strict $\alpha_{\max}$ since the population followed the optimum by stochastic jumps. This difference arises because the genetic background evolves deterministically and establishes a constant equilibrium lag. These calculations, furthermore, allow for a heuristic assessment of $\alpha_{\max}$ which increases with v and σ_s^2, but decreases with σ_g^2.

Assuming that α was deleterious prior to the environmental change, the allele frequency spectrum $\rho(x, \alpha)$, is given by equation (8). When genetic background variation is absent $\Pi_{\text{fix}}(\alpha)$ (eq. 10) can explicitly be calculated using

$$\frac{1}{\varphi_{\sigma_g^2=0}(\alpha)} = \left[1 + \frac{1}{2}\sqrt{\frac{\pi}{2\frac{\alpha v}{\sigma_s^2}}}\exp\left(\frac{s(\alpha,0)^2}{2\frac{\alpha v}{\sigma_s^2}}\right)\operatorname{erfc}\left(\frac{s(\alpha,0)}{\sqrt{2\frac{\alpha v}{\sigma_s^2}}}\right)\right]^{-1}. \tag{20}$$

For the general case, however, $\Pi_{\text{fix}}(\alpha)$ can only be calculated numerically with

$$\begin{aligned}\frac{1}{\varphi(\alpha)} &= \frac{2}{1 + \int_0^\infty 1 + s(\alpha,0)\mathrm{d}t \exp\left[-\int_0^t s(\alpha,\tau)\mathrm{d}\tau\right]} \\ &= \frac{2}{1 + \int_0^\infty (1 + s(\alpha,t)) \exp\left[-\left(\left(-\frac{\alpha^2}{2(\sigma_s^2+\sigma_g^2)}\right) + \left((1-(1-\gamma)^t)\frac{1}{\log\left[(1-\gamma)^t\right]} + 1\right)\frac{\alpha v}{\gamma(\sigma_s^2+\sigma_g^2)}\right)t\right]\mathrm{d}t}\end{aligned} \tag{21}$$

The fixation probability for an allele from the standing genetic variation with allelic effect α and a recurrent population-wide mutation rate Θ can then be calculated as

$$P_{\text{SGV}}(\alpha) = \begin{cases} 1 - C(\alpha)\int_0^1 x^{\Theta-1}\exp[-4N_e|s(\alpha,0)|x]\left(1-\frac{1}{\varphi(\alpha)}\right)^{2N_e x}\mathrm{d}x & \text{if } 0<\alpha<\alpha_{max} \\ 0 & \text{otherwise} \end{cases} \tag{22}$$

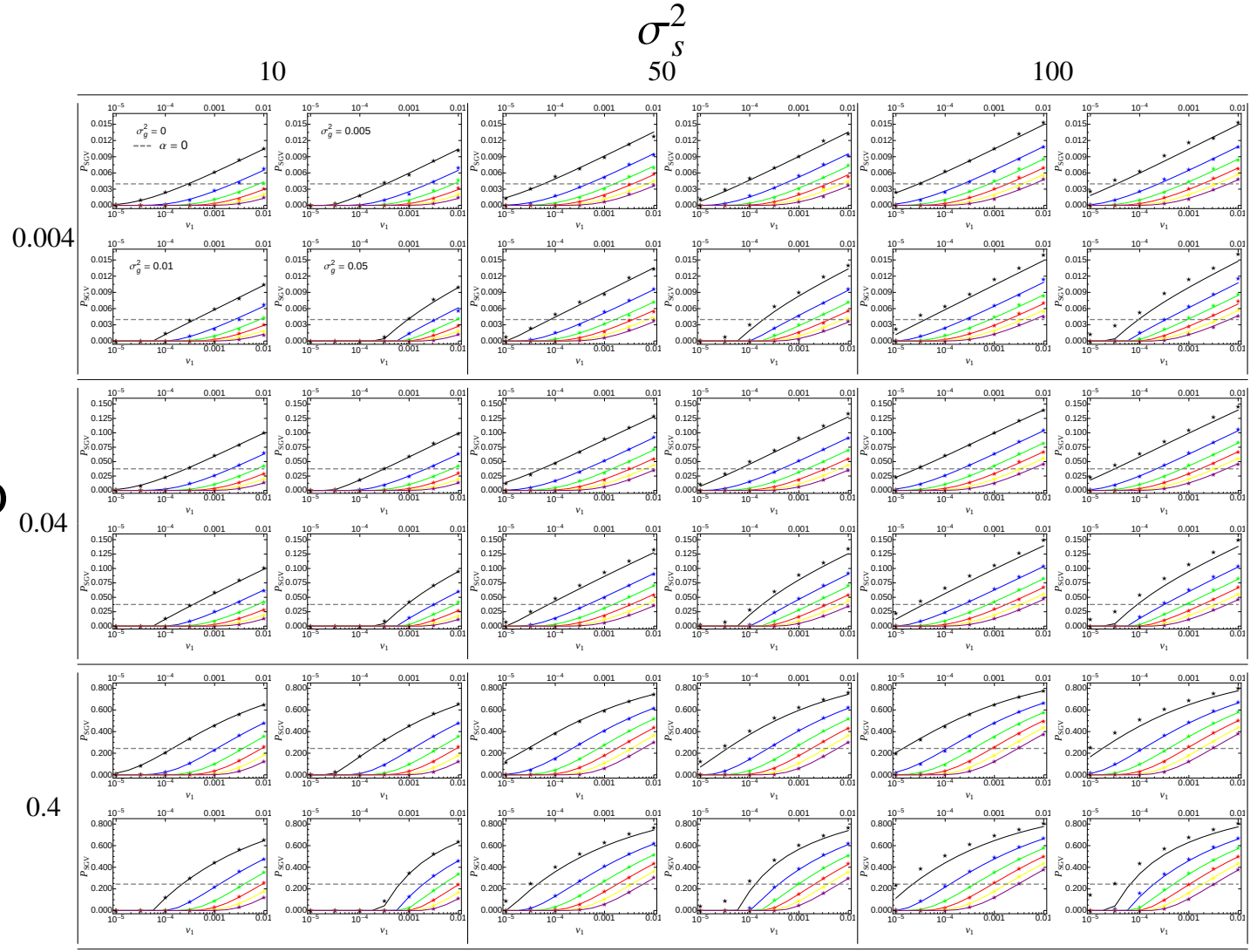
Checking our analytical approximations against Wright-Fisher simulations (for details see subsection 2.3.1) showed that they in general perform very well (Fig. 1). Only if background genetic variation is large (large σ_g^2) and the strength of stabilizing selection is weak (i.e., if σ_s^2 is large) does the analytical approximation underestimate $P_{\text{SGV}}(\alpha)$ for small $\alpha \sim 0.5\sigma_m$. The reason is that, under a constant optimum, the genetic background will compensate for the deleterious effect of α (i.e., $\bar{z}_{\text{B}} < 0$, in violation of our assumption that $\bar{z}_{\text{B}} = 0$), effectively reducing the selection strength against the deleterious mutant allele. Consequently, α on average is already present at higher frequencies than predicted by equation (8). Note that in the limit of $\alpha \ll \sigma_m$ and very slow rates of environmental change (i.e., $v \ll 10^{-5}$), $P_{\text{SGV}}(\alpha)$ will approach that for a neutral allele (i.e., $\alpha = 0$). The probability that a neutral allele is present in the population and becomes fixed can be calculated (by using equation 6) as

$$\begin{aligned}P_{\text{SGV, neutral}} &= \int_0^1 x\rho(x)\mathrm{d}x \\ &= \frac{H_\Theta - 1}{\gamma + \psi(\Theta)}\end{aligned} \tag{23}$$

where H_n denotes the n^{th} harmonic number, $\gamma \approx 0.577$ is Euler's gamma and $\psi(\bullet)$ is the polygamma function.

The results in Figure 1, furthermore, show some general trends. First, the probability for a mutant allele α to become fixed increases with Θ, σ_s^2 and v, irrespective of its effect-size. In accordance with the results from Chevin and Hospital (2008), we find that $P_{\text{SGV}}(\alpha)$ critically depends on the genetic background variation σ_g^2. In particular, as σ_g^2 increases $P_{\text{SGV}}(\alpha)$ decreases, rendering most large effect alleles deleterious even if the rate of environmental change is fast.

Figure 1 – The probability to adapt from standing genetic variation as a function of the rate of environmental change v. Solid lines correspond to the analytical prediction (eq. 22), the grey dotted line gives $P_{\text{SGV, neutral}}$ (eq. 23), and symbols give WF-simulation results. The phenotypic effect size α ranges from $0.5\sigma_m$ (top line) to $3\sigma_m$ (bottom line) with increments of $0.5\sigma_m$. The figures in each parameter box correspond to different values of σ_g^2 with $\sigma_g^2 = 0$ (no background variation; top left), $\sigma_g^2 = 0.005$ (top right), $\sigma_g^2 = 0.01$ (bottom left) and $\sigma_g^2 = 0.05$ (bottom right). Other parameters: $N_e = 25000$, $\sigma_m^2 = 0.05$.



3.2. The distribution of standing adaptive substitutions

When deriving the distribution of standing adaptive substitutions, we have to account for the fact that the individual-based simulations assume an infinite-sites model. Thus, there are no recurrent mutations, and every allele originates from a single mutation. Note that equation (22) contains a probability that the allele is not present in the population when the environment starts changing. This probability can be approximated by integrating over the distribution of allele frequencies $\rho(x, \alpha)$ from 0 to $\frac{1}{2N_e}$ (see Appendix in Hermisson and Pennings 2005) and approximately evaluates to

$$\begin{aligned} P_0(\alpha) &\approx \left(\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right)^{-\Theta} \\ &= \exp\left[-\Theta \log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]. \end{aligned} \tag{24}$$

The fixation probability for a segregating allele that is derived from a single mutation prior to the environmental change can then be derived by conditioning on segregation of the allele in the limit $\Theta \to 0$ (Hermisson and Pennings 2005). With a moving phenotypic optimum this probability reads

$$\begin{aligned} \Pi_{\text{seg}}(\alpha) &= \lim_{\Theta\to 0} \frac{P_{\text{SGV}}(\alpha)}{1 - P_0(\alpha)} \\ &\approx \lim_{\Theta\to 0} \frac{1 - C(\alpha)\int_0^1 x^{\Theta-1}\exp[-4N_e|s(\alpha,0)|x]\left(1-\frac{1}{\phi(\alpha)}\right)^{2N_e x}\mathrm{d}x}{1-\exp\left[-\Theta\log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]}. \end{aligned} \tag{25}$$

Since the numerator can only be calculated numerically, the limit in equation (25) can be approximated by replacing Θ by a placeholder variable $\epsilon \ll 1$. Multiplying by the α-specific mutation rate $\Theta p(\alpha)$ (i.e., the rate of mutations with effect α), the distribution of standing substitutions can be calculated as

$$\begin{aligned} p_{\text{SGV}}(\alpha) &\approx \frac{\Theta p(\alpha)\Pi_{\text{seg}}(\alpha)}{\int_0^{\alpha_{max}} \Theta p(\alpha)\Pi_{\text{seg}}(\alpha)\mathrm{d}\alpha} \\ &= \frac{p(\alpha)\Pi_{\text{seg}}(\alpha)}{\int_0^{\alpha_{max}} p(\alpha)\Pi_{\text{seg}}(\alpha)\mathrm{d}\alpha}. \end{aligned} \tag{26}$$

Note that while Θ does not affect the distribution of the focal allele directly (since there are no recurrent mutations), it still indirectly enters $p_{\text{SGV}}(\alpha)$ through σ_g^2. In particular, in

the SHC approximation (eq. 16) σ_g^2 scales linearly with Θ. Furthermore, equation (26) should be valid for any distribution of mutational effects $p(\alpha)$.

In the limit where the equilibrium lag is reached fast (i.e., when σ_s^2 is small and v is large) the moving-optimum model reduces to a model with constant selection (e.g., as in Hermisson and Pennings 2005). Using equations (9), (24), and (26), the distribution of standing substitutions can be approximated by

$$p_{\mathrm{SGV},\delta_{\mathrm{eq}}}(\alpha) \approx \frac{p(\alpha)\frac{1-\exp\left[-\epsilon\log\left[1+\frac{2N_e s(\alpha,\infty)}{4N_e|s(\alpha,0)|+1}\right]\right]}{1-\exp\left[-\epsilon\log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]}}{\int_0^{\alpha_{max}} p(\alpha)\frac{1-\exp\left[-\epsilon\log\left[1+\frac{2N_e s(\alpha,\infty)}{4N_e|s(\alpha,0)|+1}\right]\right]}{1-\exp\left[-\epsilon\log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]}\mathrm{d}\alpha}. \tag{27}$$

Similarly, we can calculate the limit distribution of *de-novo* substitutions as

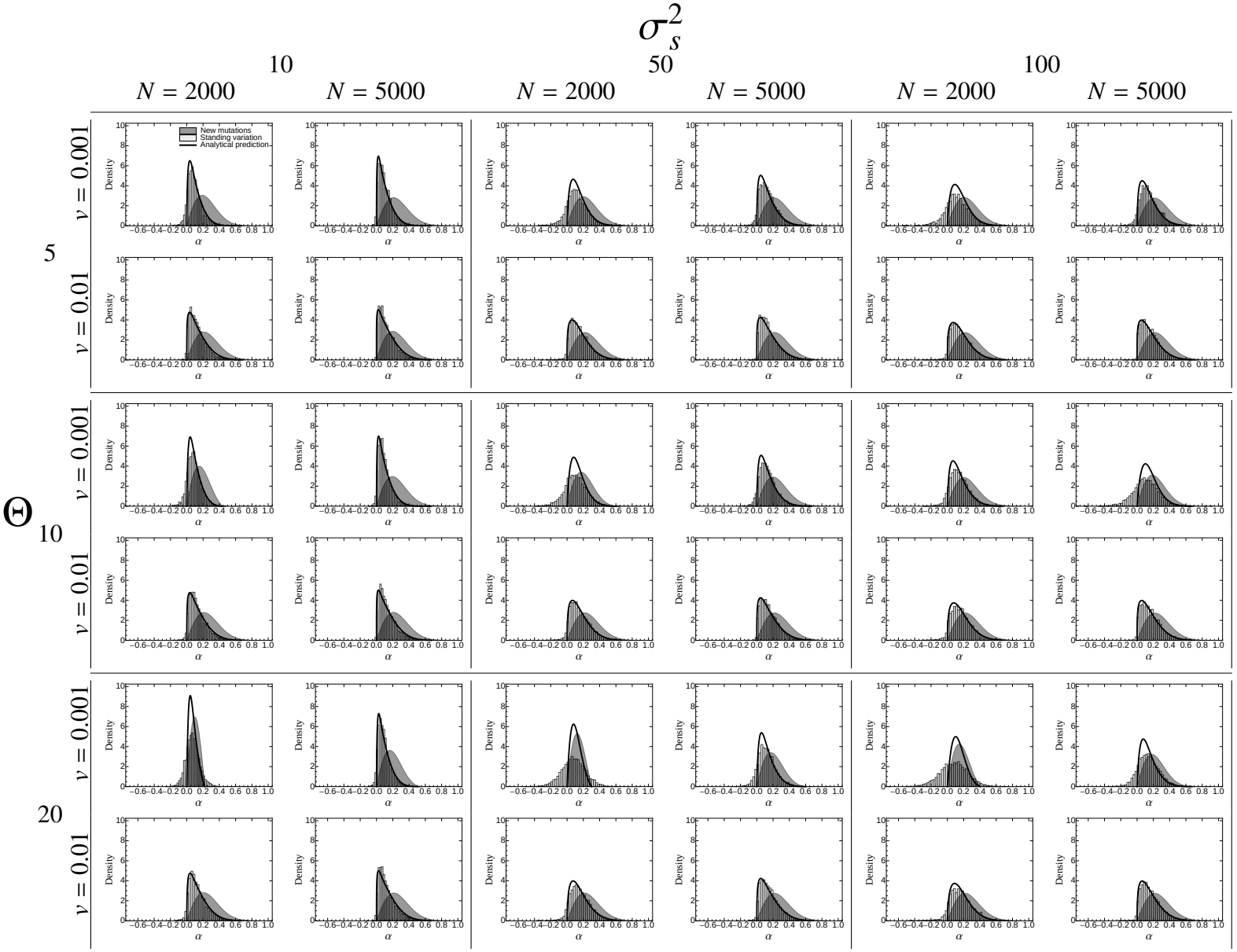
$$p_{\mathrm{DNM},\delta_{\mathrm{eq}}}(\alpha) \approx \frac{p(\alpha)\left(1-\exp\left[-\frac{\alpha(2\delta_{\mathrm{eq}}-\alpha)}{\sigma_s^2+\sigma_g^2}\right]\right)}{\int_0^{\alpha_{max}} p(\alpha)\left(1-\exp\left[-\frac{\alpha(2\delta_{\mathrm{eq}}-\alpha)}{\sigma_s^2+\sigma_g^2}\right]\right)\mathrm{d}\alpha}. \tag{28}$$

In contrast, if the environment changes very slowly, we can calculate the limit distribution of standing substitutions conditioned on segregation by using equation (7) and approximating the fixation probability by that of a neutral allele (i.e., its allele frequency)

$$p_{\mathrm{SGV},v_0}(\alpha) \approx \frac{\frac{p(\alpha)C(\alpha){}_1F(0,\epsilon+1,4N_e|s(\alpha,0)|}{1-\exp\left[-\epsilon\log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]}}{\int_{-\infty}^{\infty}\frac{p(\alpha)C(\alpha){}_1F(0,\epsilon+1,4N_e|s(\alpha,0)|}{1-\exp\left[-\epsilon\log\left[\frac{2N_e}{4N_e|s(\alpha,0)|+1}\right]\right]}\mathrm{d}\alpha} \tag{29}$$

where $C(\alpha) = ({}_1F(0,\epsilon,4N_e|s(\alpha,0)|))^{-1}$ denotes a normalization constant. Note that the integral in the denominator can be approximated by sufficiently large boundaries (e.g., $\pm 3\sigma_m$). Furthermore, unlike equation (26), this approximation (eq. 29) permits to predict substitutions with negative allelic effects (i.e., $\alpha < 0$).

Figure 2 – The distribution of adaptive substitutions from standing genetic variation compared to that from *de-novo* mutations (eq. 28). The black line corresponds to the analytical prediction (eq. 26). σ_g^2 is given by equation (16). Other parameters: $\sigma_m^2 = 0.05$.



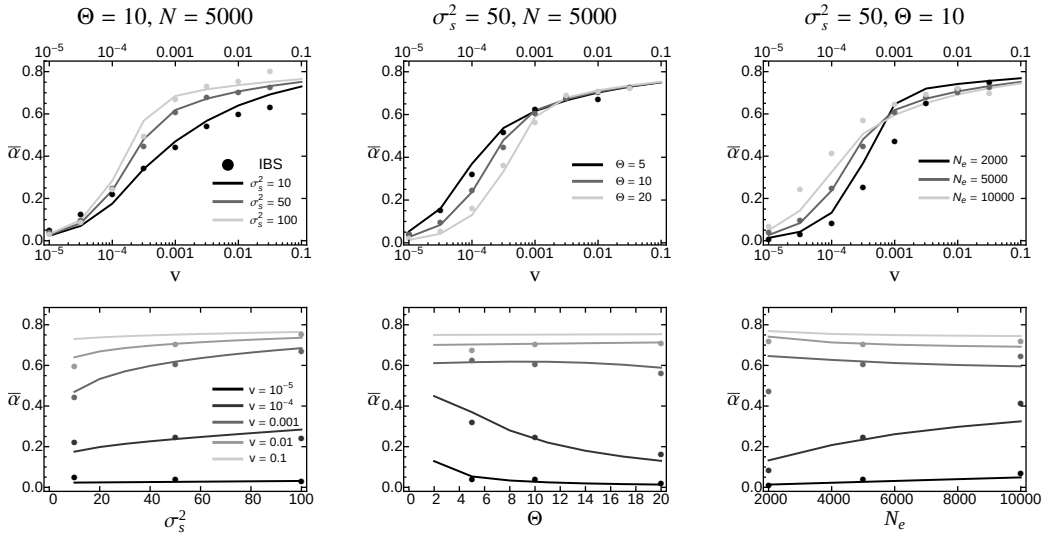


Figure 3 – The analytical approximation of the mean step size $\bar{\alpha}$ ($\int_0^{\alpha_{\max}} \alpha p_{\mathrm{SGV}}(\alpha)\mathrm{d}\alpha$) measured in units of σ_m as a function of the rate of environmental change v (top row) and for various v as a function of σ_s^2 (bottom left), Θ (bottom middle) and N_e (bottom right). Symbols give the individual-based simulation results. Individual-based simulation results for $v = 0.1$ constitute a degenerate case and are thus not shown (for details see The accuracy of the approximation). Other parameters: $\sigma_m^2 = 0.05$.

Figure 4 – The distribution of adaptive substitutions from standing genetic variation compared to that from *de-novo* mutations (eq. 28) for various rates of environmental change. The black line corresponds to the analytical prediction (eq. 26). σ_g^2 is given by equation (16). Other parameters: $\Theta = 5$, $N = 5000$, $\sigma_m^2 = 0.05$.

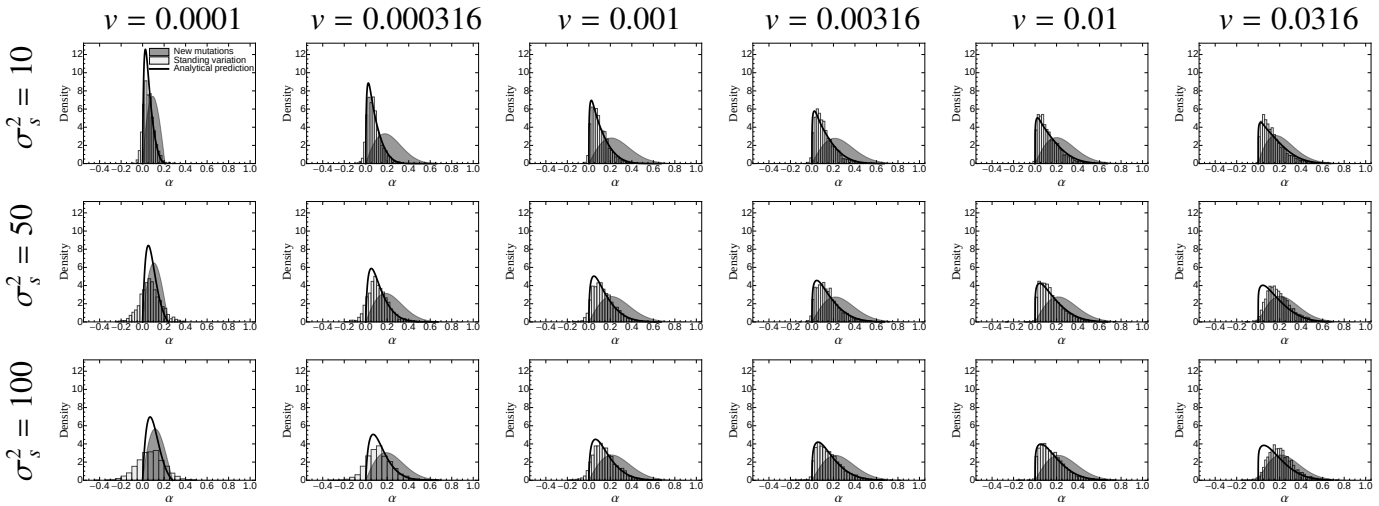
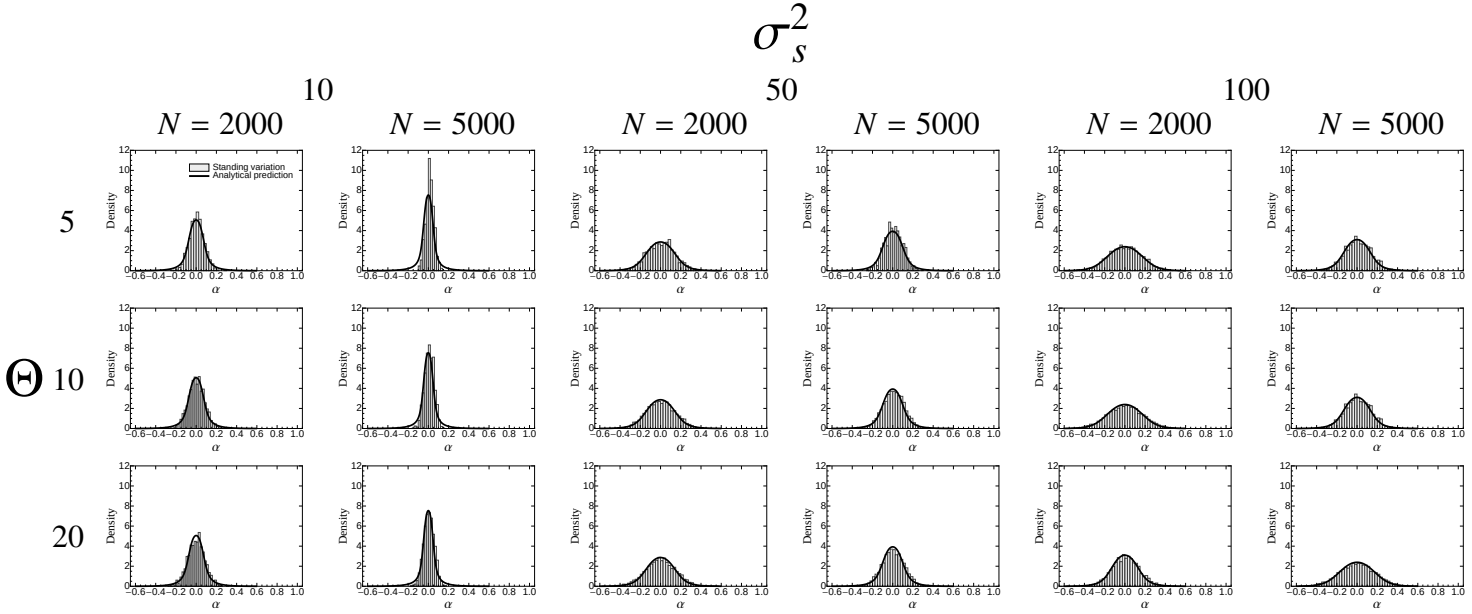


Figure 5 – The distribution of adaptive substitutions from standing genetic variation compared to the analytical prediction (black line; eq. 29). σ_g^2 is given by equation (16). Other parameters: $v = 10^{-5}$, $\sigma_m^2 = 0.05$.



The distribution of adaptive substitutions from standing genetic variation (Figs. 2,4) has an intermediate mode and resembles a log-normal distribution. Compared to adaptive substitutions from *de-novo* mutations, substitutions from standing genetic variation have smaller effects. Furthermore, as for *de-novo* mutations, the mean phenotypic effect of substitutions increases with the rate of environmental change (Fig. 3, top row). In particular, as v increases, there are fewer "backward-steps" (i.e., substitutions with negative effect that are opposite to the moving direction; Fig. 4), while at the same time larger phenotypic effects can become fixed. Additionally, if the rate of environmental change is fast, the distribution of standing substitutions becomes more skewed, resembling the "almost exponential" distribution of *de-novo* substitutions in the sudden change scenario (Orr 1998). Interestingly, in contrast to the effect-size distribution of fixed *de-novo* mutations, even though the mean increases, the mode of the distribution of standing substitutions shifts towards smaller values as v increases (i.e., the distribution becomes more asymmetric; Fig. 4). Recall that the effect-size distribution of standing substitutions is ultimately the product of the allele-frequency spectrum $\rho(x, \alpha)$ and the corresponding fixation probabilities $\Pi_{\text{fix}}(\alpha)$ (eq. 4). Of course, only the latter depends on v. As long as the rate of environmental change is slow, most alleles get fixed or lost simply by chance (i.e., genetic drift), because selection is not efficient enough. As v increases, so does the selection coefficient of all positive mutations. Thus, more alleles need to pass the selective sieve (*sensu* Kopp and Hermisson 2009b) to become fixed.

The rate of environmental change v has a strong impact on how the distribution of standing substitutions, and in particular, its mean $\bar{\alpha}$ depends on the rate of mutational supply Θ. Recall that Θ only indirectly enters $p_{\text{SGV}}(\alpha)$ through σ_g^2. Accordingly, as Θ increases so does σ_g^2 and, thus, γ (eq. 15b). In the limit $t \to \infty$, the population will follow the optimum at a constant lag $\delta_{eq} = \frac{v}{\gamma}$. Thus, if v is large (and the lag is large even for large σ_g^2) increasing Θ does not affect $\bar{\alpha}$. In contrast, if v is small, increasing the genetic background variation (by increasing Θ) will reduce the lag even further, making most large-effect alleles deleterious. Consequently, for small v, $\bar{\alpha}$ decreases as Θ increases (Fig. 3).

The width of the fitness landscape of σ_s^2 is more ambiguous, as it affects different aspects of the adaptive process. First, as σ_s^2 increases (i.e., as stabilizing selection gets weaker) alleles start at higher average initial frequencies. In particular, the amount of large-effect alleles in the standing genetic variation increases, as selection gets less efficient in purging them. On the other hand, the same effect also increases the amount of genetic background variation σ_g^2, which might prevent most large-effect alleles from becoming beneficial. Second, also the strength of directional selection (after the optimum starts

moving) decreases with that of stabilizing selection (Kopp and Matuszewski 2014). Consequently, s_t (the rate of selection coefficient increase; second term in eq. 14) decreases as stabilizing selection gets weaker. Overall, however, we find that the mean fixed phenotypic effect increases with σ_s^2 (Fig. 3). The reason is, that the inefficiency of selection also results in an increased equilibrium lag, which together with the increased starting frequency outweighs disadvantage of the smaller s_t and the increased σ_g^2.

Similar arguments hold for N_e (when Θ is held constant). First, increasing N_e will always increase the efficacy of selection, resulting in lower initial starting frequencies of mutant alleles (eq. 7) and decreased σ_g^2 (eq. 16). If the environment changes slowly, $\bar{\alpha}$ increases with N_e, because the equilibrium lag increases (caused by the decrease in σ_g^2). In contrast, if the rate of environmental change is fast, $\bar{\alpha}$ slightly decreases due to the lower initial starting frequency and because small-effect alleles are selected for more efficiently (i.e., they are less prone to get lost by genetic drift, since $N_e s$ increases).

The accuracy of the approximation. In our analytical derivations, we have used different results derived from both diffusion theory and branching processes. When compared to our individual-based simulations of an explicit genetic model, we find that the performance of our approximations is often surprisingly good as long as selection is strong, i.e., if v is large and/or the strength of stabilizing selection σ_s^2 is not too weak. Conversely, if selection is weak our analytically-derived distribution (eq. 26) fails to capture the shape of the distribution. This discrepancy arises since we condition on $s(\alpha, t)$ to be positive for large t for alleles to become fixed. Thus, neutral alleles ($\alpha = 0$) and 'backward steps' (i.e., $\alpha < 0$; e.g., Fig. 2) are not captured by our analytically derived distribution (eq. 26). Particularly, if genetic drift is the main driver of phenotypic evolution (e.g., if the environment changes very slowly), the distribution of standing substitutions resembles a Gaussian distribution with its mean slightly offset from 0, including a lot of backward steps. Indeed, equation (29) provides a very good fit to our individual-based simulations (Fig. 5) when the overall strength of selection is low, i.e., when $N_e|s(\alpha, t)| < 1$. Recall, however, that $N_e s(\alpha, t)$, depends itself on v, σ_s^2 and σ_g^2.

With a moving phenotypic optimum the selection coefficient (eq. 17) increases with time. Accordingly, there is always a phase during the adaptive process where genetic drift dominates, i.e., where $N_e|s(\alpha, t)| < 1$. The length of this phase (i.e., the time it takes until selection becomes the main force of evolution) again depends on the interplay of multiple parameters, notably α, v, σ_s^2, N_e and Θ. A good heuristic to identify the main driver of phenotypic evolution is to calculate $N_e s_{\max}$ (eq. 19), which gives the maximal population-scaled selection coefficient. Since the selection coefficient of most mutations

will be smaller, one can consider as a rule of thumb that drift is the main driver of evolution as long as $N_e s_{\max} \leq 10$. Similarly, when $N_e s_{\max} > 10$ equation (26) matches the individual-based simulations very well. In summary, the accuracy of our approximation crucially depends on the efficacy of selection.

Interestingly, if the environment changes very fast the distribution of standing substitutions from our IBS almost exactly matches the one for *de-novo* mutations (Fig. 6). However, this seems to be an artifact rather than a relevant biological effect. The reason is that the environment changes so fast that the population quickly dies out. Thus, the resulting distribution of standing substitutions is that for a dying population and might not necessarily reflect the adaptive process. In an experimental setup, though, where populations evolve until they go extinct, the distribution of adaptive standing substitutions might be indistinguishable to the distribution from *de-novo* mutations.

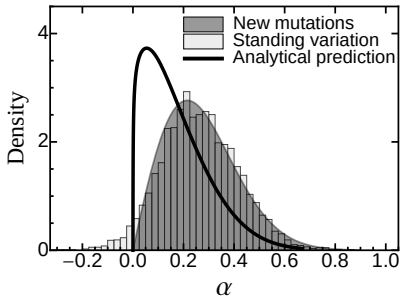


Figure 6 – The distribution of adaptive substitutions from standing genetic variation compared to that from *de-novo* mutations (eq. 28). The black line corresponds to the analytical prediction (eq. 26). σ_g^2 is given by equation (16). Other parameters: $\sigma_s^2 = 100$, $\Theta = 20$, $N = 5000$, $v = 0.1$, $\sigma_m^2 = 0.05$.

3.3. Extinction and the rate of environmental change

Even though not the main focus of the present study, we also performed individual-based simulations to investigate the relation between the rate of environmental change and population extinction when adaptation depends exclusively on standing genetic variation (i.e., when there are no further mutations after the environmental change). For this purpose, we recorded the mean population phenotype $\bar{z}$ at the time standing genetic variation was exhausted (i.e., when all alleles had been either fixed or lost). This amount of phenotypic evolution from standing genetic variation alone determines the amount of environmental change the population can tolerate before extinction becomes inevitable without the input of new mutations (i.e., before the phenotypic lag becomes so large that the population mean fitness drops below a critical value). Our simulation results show that the average distance traversed in phenotype space initially increases with the rate of environmental change, until v becomes very fast where it drops off sharply (Fig. 7).

The reason is that more (large-effect) alleles become fixed as v increases until the rate of environmental change becomes so fast, that the population goes extinct even before all positively selected alleles can become fixed. Conversely, this means that if the optimum stopped moving at a given value $z_{\text{opt,max}}$ (e.g., the maximal possible $\bar{z}$), populations will achieve a higher degree of adaptation (higher $\bar{z}^*$) if the final optimum is reached fast rather than slowly, at least if standing genetic variation is the sole source for adaptation. Note that this pattern is qualitatively consistent across different values of σ_s^2 and Θ (Fig. 7). Clearly, the assumption of no new mutations appearing after the environmental change is an evident simplification. In experimental populations, however, where selection is strong and the duration of the experiment is usually short, *de-novo* mutations can often be neglected.

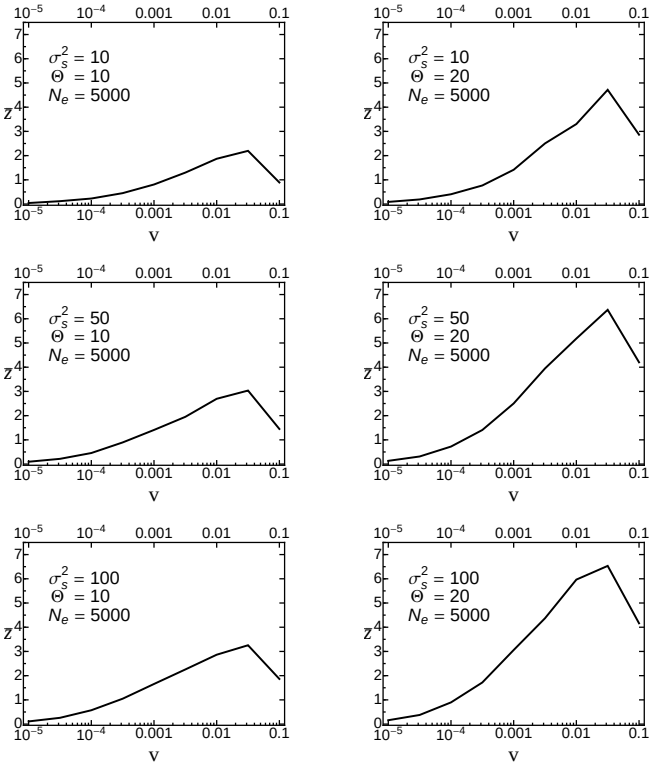


Figure 7 – The average distance traversed in phenotype space as a function of the rate of environmental change v when standing genetic variation is the sole source for adaptation (i.e., there were no new mutations after the environment started changing). σ_g^2 is given by equation (16). Data points from individual-based simulations are averaged over 100 replicate runs. Other parameters: $\sigma_m^2 = 0.05$.

4. Discussion

Global climate change has forced many populations to adapt to the altered environmental conditions to avoid extinction. When studying the genetic basis of this process, most theoretical work has focused on adaptation from new mutations (Gillespie 1984; Orr 1998, 2000; Collins et al. 2007; Kopp and Hermisson 2007, 2009a,b; Matuszewski et al. 2014). Consequently, very little is known about the genetic basis of adaptation from standing genetic variation (but see Hermisson and Pennings 2005), that is, which of the alleles segregating in the population will become fixed and contribute to adaptation. Here, we have used analytical approximations and stochastic simulations to study the effects of standing genetic variation on the genetic basis of adaptation in gradually changing environments. Supporting Barrett and Schluter (2008), we show that, compared to *de-novo* mutations, adaptation from standing genetic variation proceeds, on average, by smaller steps (i.e., by the fixation of more alleles of small effect). As in adaptive-walk models, however, the genetic basis of adaptation from standing genetic variation crucially depends on the efficacy of selection, which in turn is determined by the population size, the strength of (stabilizing) selection and the rate of environmental change. When standing genetic variation is the sole source for adaptation, we find that fast environmental change enables the population to traverse larger distances in phenotype space than under slow environmental change, thus contrasting studies that consider adaptation from new mutations only (Perron et al. 2008; Bell and Gonzalez 2011; Lindsey et al. 2013; Bell 2013). We now discuss these results in greater detail.

4.1. Adaptation in the moving optimum model

Introduced as a model for sustained environmental change, such as global warming (Lynch et al. 1991; Lynch and Lande 1993), the moving-optimum model describes the evolution of a quantitative trait under stabilizing selection towards a time-dependent optimal phenotype (Bürger 2000). A large number of studies have analyzed both the basic model and several modifications, for example, models with a periodic or fluctuating optimum, or models for multiple traits (Slatkin and Lande 1976; Charlesworth 1993; Bürger and Lynch 1995; Lande and Shannon 1996; Kopp and Hermisson 2007, 2009a,b; Gomulkiewicz and Houle 2009; Zhang 2012; Chevin 2013; Matuszewski et al. 2014). Following traditional quantitative-genetic approaches, the majority of these studies, however, assumed that the distribution of genotypes (and phenotypes) follows a Gaussian

with constant (time-invariant) genetic variance and have mostly focussed on the evolution of the population mean phenotype and population persistence in changing environments (Bürger and Lynch 1995; Lande and Shannon 1996; Gomulkiewicz and Houle 2009). None of these models, however, allows to address the fate of individual alleles (i.e., whether they become fixed or not). In a recent series of papers Kopp and Hermisson (2007, 2009a,b) studied the genetic basis of adaptation from new mutations and derived the distribution of adaptive substitutions (i.e, the distribution of those mutations that arise in population and become fixed); this approach has recently been generalized to multiple phenotypic traits (Matuszewski et al. 2014). The shape of this distribution resembles a Gamma-distribution with an intermediate mode. Thus, most substitutions are of intermediate effect with only a few large-effect alleles contributing to adaptation. The reason is that small-effect alleles – despite appearing more frequently than large-effect alleles – only have small effects on fitness and, hence, are often lost due to genetic drift, while large-effect alleles might be removed because they "overshoot" the optimum (Kopp and Hermisson 2009b).

Similarly to Kopp and Hermisson (2009b), we find that the distribution of standing substitutions depends on the distribution of standing genetic variants (i.e., the distribution of alleles segregating in the population prior to the environmental change) and the intensity of selection. The distribution of standing genetic variants is shaped primarily by the strength of stabilizing selection, which removes large-effect alleles. In contrast, the influence of the distribution of new mutations is relatively weak, since for a sufficient number of loci, the distribution of standing variants will always converge to a Gaussian (Lande 1976). After the environmental change, the standing genetic variation is "filtered" by selection. Depending on the speed of change v, we find two regimes characterized by a separate distribution. If v is very small, allele-frequency dynamics are dominated by genetic drift, and the distribution of standing substitutions reflects the approximately Gaussian distribution of standing genetic variants (eq. 29; Fig. 5). Conversely, if the environment changes fast, selection will become the main driver of phenotypic evolution and transform the distribution of standing genetic variants into an log-normal-like distribution of standing substitutions (eq. 26; Fig. 2). Consequently, when adapting from standing genetic variation, most substitutions are of small phenotypic effect. The reason is that, in the standing genetic variation, small-effect alleles are more frequent than large-effect alleles and might already segregate at appreciable frequency (so that they are not lost by genetic drift). With a moving optimum, they furthermore are the first

to become positively selected, hence reducing the time they are under purifying selection. Thus, compared to adaptation from *de-novo* mutations, adaptation from standing variation proceeds by the fixation of more alleles of small effect.

4.2. Connection to experimental data

Recently, several experimental studies have explored how the rate of environmental change affects the persistence of populations adapting to a gradually changing environment (Perron et al. 2008; Bell and Gonzalez 2011; Lindsey et al. 2013). In line with theoretical predictions (Bell 2013), all studies found that evolutionary rescue is contingent on a small rate of environmental change. In particular, Lindsey et al. (2013) evolved replicate populations of *E. coli* under different rates of increase in antibiotic concentration and found that certain genotypes were evolutionarily inaccessible under rapid environmental change, suggesting that "rapidly deteriorating environments not only limit mutational opportunities by lowering population size, but [...] also eliminate sets of mutations as evolutionary options". This is in contrast to our prediction that faster environmental change can enable the population to remain better adapted and to traverse larger distances in phenotype space, when standing genetic variation is the sole source for adaptation (Fig. 7; in line with recent experimental observations; H. Teotonio, private communication). The difference between these results arises from the availability of the "adaptive material". While standing genetic variants are on-hand right away and might already be segregating at appreciable frequency, *de-novo* mutations first need to appear and survive stochastic loss before becoming fixed. Thus, in both cases, the rate of environmental change plays a critical, though antagonistic, role in determining the accessibility of the adaptive material as evolutionary options. While fast environmental change eliminates sets of new mutations, it simultaneously helps to preserve standing genetic variation until it can be picked-up by selection. Under slow change, in contrast, most large-effect alleles from the standing variation, by the time they are needed, will already have been eliminated by drift or purifying selection.

4.3. Testing the predictions

The predictions made by our model can in principle be tested empirically, even though suitable data might be sparse and experiments challenging. There is, of course, ample evidence for adaptation from standing genetic variation. For example, Domingues et al. (2012) showed that camouflaging pigmentation of oldfield mice (*Peromyscus polionotus*) that have colonized Florida's Gulf Coast has evolved quite rapidly from a preexisting

mutation in the *Mc1r* gene; Limborg et al. (2014) investigated selection in two allochronic but sympatric lineages of pink salmon (*Oncorhynchus gorbuscha*) and identified 24 divergent loci that had arisen from different pools of standing genetic variation, and Turchin et al. (2012) showed that height-associated alleles in humans display a clear signal for widespread selection on standing genetic variation.

Furthermore, testing the predictions of our model requires detailed knowledge of the genotype-phenotype relation. Currently, there is only a small (though increasing) number of cases for which both a set of functionally validated beneficial mutations and their selection coefficients under different environmental conditions are available (Jensen 2014). Recent developments in laboratory systems (Morran et al. 2009; Parts et al. 2011), however, have created opportunities for experimental evolution where population size, the selective regime and the duration of selection can be manipulated, and which allow adaptation from *de-novo* mutations and standing genetic variation to be recorded (Burke 2012). Applying these techniques in experiments in the vein of Lindsey et al. (2013) but starting from a polymorphic population should make it possible to test the relation between the rate of environmental change and population persistence, and to assess the probability to adapt from standing genetic variation. First experiments along these lines are currently being carried out in populations of *C. elegans*, with the aim of determining the limits of adaptation to different rates of increase in sodium chloride concentration (H. Teotonio, private communication). Encouragingly, Pennings (2012) recently applied the Hermisson and Pennings (2005) framework to study the evolution of drug resistance in *HIV* from standing genetic variation and found that the model provided explanations for why resistance mutations in women who only receive a single-dose treatment, and patients who interrupt treatment, are likely to become established within the first year. This study, furthermore, emphasized that standing genetic variation plays an important role in the evolution of drug-resistance, affecting up to 39% of patients (depending on treatment).

Estimating the distribution of standing substitutions will be even more challenging, because of the often unknown genotype-phenotype relation of beneficial mutations and the large number of replicate runs needed to obtain a reliable empirical distribution. Furthermore, even if these problems were solved, small-effect alleles might not be detectable due to statistical limitations (Otto and Jones 2000), and in certain limiting cases where the population quickly goes extinct (i.e., when the environment changes very fast), the distribution of standing substitutions might be indistinguishable from the distribution of *de-novo* substitutions (Fig. 6).

4.4. Future directions

Here, we have used an approach originally proposed by Lande (1983), which considers the simultaneous evolution at a focal locus and of genetic background variation (mimicking the collective selective response across other loci) and still allows to obtain an analytically tractable model. When compared to our individual-based simulations with an explicit multi-locus genetic context, we obtained an surprisingly good description of the adaptive process. One key assumption, however, is that the focal allele and the genetic background are in linkage equilibrium (i.e., that there is free recombination). An obvious follow-up question would be how linkage (i.e., limited recombination) affects the distribution of standing substitutions. Considering adaptation from *de-novo* mutations, Kopp and Hermisson (2009b) and Matuszewski et al. (2014) found that increased linkage increases the mean size of adaptive substitutions in the moving-optimum model. The reason are interference effects between co-segregating alleles (e.g., Hill-Robertson interference; Hill and Robertson 1966) that reduce the efficacy of selection (Gerrish and Lenski 1998; Weissman and Barton 2012). This aspect should still hold true for adaptation from standing genetic variation and might even be reinforced, since linkage also reduces the (standing) genetic variance σ_g^2 (Bürger 1989). On the other hand, large-effect alleles are rarer in the standing genetic variation, which might counteract or even override the former effect, depending on the genetic and ecological parameters.

Furthermore, it might be interesting to see how our results for a moving phenotypic optimum relate to the case of a sudden environmental change. For adaptation from *de-novo* mutations Kopp and Hermisson (2009b) and Matuszewski et al. (2014) showed that the mode of environmental change plays a critical role for the genetic basis of adaptation. This should still be expected for adaptation from standing genetic variation. In particular, unlike in the moving-optimum model where the phenotypic lag (and thus the selection coefficient) increases monotonically, adaptation to a constant optimum is characterised by a decreasing lag. Hence, in the presence of genetic background variation, alleles need to "race for fixation" before other competing alleles get fixed and they become deleterious. The dynamics of a mutation along its trajectory should therefore be even more complex than in the moving-optimum model, and expected to show an even stronger dependence on the genetic background (Chevin and Hospital 2008).

Finally, while we have compared adaptation from standing genetic variation to that from new mutations (though focussing on the former), we have not investigated their relative importance during the course of adaptation. Although pioneering work by Hill (1982b,a) and Hill and Rasbash (1986b) yielded some general results concerning the response to

selection due to new mutations in a quantitative-genetics framework – the latter work even explicitly considering both new mutations and standing genetic variation – the relative role of standing genetic variation versus new mutations during short- and medium-term adaptation needs to addressed in future studies.

4.5. Conclusion

As global climate change continues to force populations to respond to the altered environmental conditions, studying adaptation to changing environments – both empirically and theoretically – has become one of the main topics in evolutionary biology. Despite increased efforts, however, very little is known about the genetic basis of adaptation from standing genetic variation. Our analysis of the moving-optimum model shows that this process has, indeed, a very different genetic basis than that of adaptation from *de-novo* mutations. In particular, adaptation proceeds in many small steps and just a few large ones. In accordance with previous studies, the adaptive process critically depends on the tempo of environmental change. Specifically, when populations adapt from standing genetic variation only, the prospects of population persistence increase as the environment changes faster.

Acknowledgements

This study was supported by Austrian Science Fund, FWF (grant P 22581-B17) to MK and FWF (grant P22188) to Reinhard Bürger, Austrian Agency for International Cooperation in Education and Research, OEAD (grant FR06/2014) to JH, and a Writing-Up Fellowship from the Konrad Lorenz Institute for Evolution and Cognition Research to SM. The computational results presented have been achieved in part using the Vienna Scientific Cluster (VSC).

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Information about submission and S. Matuszewski's contribution

STATUS:	in preparation
JOURNAL:	Genetics

S. MATUSZEWSKI'S CONTRIBUTION: Contributed to the model design, derived the numerical and the analytical results, wrote simulation code and the manuscript draft.

Zusammenfassung in deutscher Sprache

> "As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be naturally selected. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form."
>
> — Charles Darwin, *The Origin of Species*

Genetische Anpassung ist die Triebfeder der Darwin'schen Evolution. Um nicht auszusterben, müssen sich natürliche Populationen ihren Umwelten anpassen. Dieser Punkt ist im besonderen Maße im Zuge des globalen Klimawandels akut geworden, welcher eine Vielzahl von Populationen Veränderungen der Temperatur, der Luftfeuchte und saisonalen Gegebenheiten ausgesetzt hat. Während von Menschen verursachte Klimaveränderungen viele Populationen an den Rand des Aussterbens gedrängt haben, ist es anderen gelungen, sich an die neuen Bedingungen anzupassen. Seit 1975 sind 12% der lokalen mexikanischen *Sceloporus* Eidechsen-Populationen ausgestorben. Sollten die heliothermen Reptilien es weiterhin nicht schaffen ihre thermale Physiologie an die steigenden Temperaturen anzupassen, so sagen physiologische Modelle eine Aussterberate von 39% bis zum Jahr 2080 vorher (Sinervo et al. 2010). Im Gegensatz dazu haben es Darwinfinken innerhalb kürzester Zeit geschafft, sich trotz des Rückgangs der lokalen Population auf Daphne Island um 85%, an die Folgen einer extremen Dürre anzupassen (Grant und Grant 2006). Während die Zahl empirischer Studien zum Thema Anpassung in sich verändernden Umwelten kontinuierlich zunimmt, standen theoretische Untersuchung des Anpassungsprozesses dem bis vor Kurzem deutlich nach. Als Folge dessen sind Antworten zu den vermeintlich einfachsten Fragen und selbst den simpelsten Szenarien unbekannt. Beispielsweise, welche der in einer Population auftretenden Mutationen fixieren und was ist deren phänotypischer- beziehungsweise Fitnesseffekt. Können wir vorhersagen, welche Populationen das Potenzial haben, sich an schnell verändernde Umwelten anzupassen, und welche genetischen und ökologischen Faktoren den Anpassungsprozess

beschleunigen oder einschränken? Welche Bedeutung hat „stehende“ genetische Variation (das heißt Allele, die bereits in der Population segregieren) im Vergleich zu Neumutationen während kurz- und mittelfristiger genetischer Anpassung, und worin unterscheiden sich diese? Die übergeordnete Fragestellung dieser Dissertation ist daher sehr allgemein gefasst: Wie passen sich Populationen in sich verändernden Umwelten genetisch an? Spezielles Augenmerk liegt in diesem Zusammenhang auf dem Wechselspiel zwischen den evolutionären Kräften, Selektion, Mutation und Rekombination sowie den ökologischen Faktoren, wie der Art und Geschwindigkeit der Umweltänderung, und deren gemeinsame Effekte auf die Genetik des Anpassungsprozesses.

In den vergangen Jahren haben viele Studien versucht, einen formalen Rahmen zur Beschreibung des Anpassungsprozesses zu finden. Viele dieser Studien bauen auf zwei komplementären Modellierungsansätzen auf. Ein erster Ansatz fokussiert auf die statistischen Eigenschaften von adaptiven Substitutionen (das sind vorteilhafte Mutationen, welche im Zuge der genetischer Anpassung fixieren) anstatt auf Genotyp- oder Allelfrequenzdynamiken. Viele Modelle basieren entweder auf Fishers geometrischem Modell (Fisher 1930; Orr 1998, 2000; Martin und Lenormand 2006a) oder sogenannten „adaptive-walk“ beziehungsweise Mutationslandschaftsmodellen (Gillespie 1984; Kauffman und Levin 1987; Orr 2002), welche im Allgemeinen das einfachste aller möglichen Szenarien der Umweltveränderung betrachten: Die Anpassung einer Population an ein konstantes phänotypisches Optimum nach einer plötzlichen Umweltänderung. Erstaunlicherweise hat Fishers geometrisches Modell trotz seiner Einfachheit und des Fehlens eines explizit genetischen Kontextes mehr als 80 Jahre nach seiner Veröffentlichung mehrere robuste Vorhersagen geliefert, welche zunehmend durch empirische Studien bestätigt werden (Martin und Lenormand 2006a,b, 2008). Allerdings nehmen diese Modelle typischerweise an, dass Selektion stark im Vergleich zu Mutation ist, so dass die Population zu jedem Zeitpunkt nur aus einem Phäno- beziehungsweise Genotyp besteht und Evolution folglich das alleinige Produkt von Neumutationen ist.

Im starken Kontrast dazu stehen quantitativ-genetische Modelle, welche annehmen, dass genetische Anpassung einzig durch bereits existierende genetische Variationen voranschreitet. Darüber hinaus wird angenommen, dass evolvierende Merkmale eine polygene Basis haben, wobei viele Genorte jeweils verschwindend geringe Effekte haben und die Verteilung der Genotypen daher ungefähr einer Gaussverteilung folgen (Bulmer 1980; Barton und Turelli 1991; Kirkpatrick et al. 2002). Aus historischen Gründen – quantitativ-genetische Modelle waren dafür gedacht und wurden seit je her erfolgreich zur Erstellung und Optimierung von Kreuzungsschemata für Pflanzen- und Nutztierhaltung verwendet – war der Fokus dieser Modelle allerdings auf die Vorhersage von

kurzfristigen Änderungen des mittleren Phänotyps $\Delta\bar{z}$ nach einer Generation von Selektion gerichtet, anstatt auf Allelfrequenzdynamiken an einzelnen Genorten. Insbesondere kann die Änderung des mittleren Phänotyps nach einer Generation von Selektion durch die Lande-Gleichung (Lande 1976) einfach vorhergesagt werden

$$\Delta\bar{z} = \sigma_g^2\beta, \tag{1}$$

wobei σ_g^2 die additiv-genetische Varianz und β den Selektionsgradienten bezeichnet. Die wiederholte Anwendung der Lande-Gleichung erfordert jedoch, dass die Verteilungen der Phäno- und Genotypen gaussverteilt bleiben und σ_g^2 konstant ist. Während dies über kurze Zeitspannen ungefähr zutreffen mag, so ist σ_g^2 jedoch über längere Zeit, insbesondere, wenn man Anpassung an kontinuierlich fortschreitende Umweltänderung untersucht, selbst Gegenstand von evolutionärer Veränderung und hängt stark vom Input von Neumutationen ab.

Um unser Verständnis des Anpassungsprozesses und die Frage, wie sich Populationen an sich verändernde Umweltbedingungen anpassen, zu erweitern, ist es notwendig, eine Theorie aufzustellen, „die auf der Basis von empirischen Daten beruht, das heißt auf individuellen Mutationen mit individuellen Effekten“[1] (Orr 2005a); Daten, die sowohl Neumutationen als auch stehende genetische Variation umfassen. Das Schließen der Lücke zwischen „adaptive-walk“ und quantitativ-genetischen Modellen, welche die beiden Extreme eines Kontinuums von Modellierungsansätzen des genetischen Anpassungsprozesses darstellen, ist daher ein notwendiger und wichtiger Schritt zu einer allgemeinen Theorie des Anpassungsprozesses.

Ein weiterer Aspekt, der bisher überwiegend ignoriert wurde, ist, dass Anpassung letztlich die evolutionäre Konsequenz von Umweltänderungen ist – ein von Natur aus dynamischer Prozess. Während sich die Mehrheit der Studien auf das einfachste der möglichen Szenarien fokussiert, das heißt, eine einmalige plötzliche Änderung der Umwelt, ist die Notwendigkeit Modelle zu entwickeln, die kontinuiuerliche Umweltänderungen beschreiben, seit Langem bekannt (Maynard Smith 1976). So betonte Collins (2011) kürzlich, dass „die Verwendung von Modellen, welche eine plötzliche Umweltänderung annehmen, um genetische Anpassung in sich kontinuierlich verändernden Umwelten zu verstehen, nicht nur den Umfang der genetischen Anpassung unterschätzen, sondern

[1] “that speaks in the same terms as the data; that is in term of individual mutations that have individual effects”

auch die falschen geno- und phänotypischen Veränderungen vorhersagen.“[2] Diese Diskrepanz wird besonders im Hinblick auf die Konservationsbiologie offenbar. Während in den letzten beiden Jahrzehnten klar geworden ist, dass evolutionäre Veränderungen schnell genug sind, um sie in gegenwärtigen Populationen zu beobachten (Hendry und Kinnison 1999; Collins et al. 2007; Lindsey et al. 2013), bleibt die Hauptfrage, ob genetische Anpassung schnell genug ist, damit Populationen mit den sich verändernden Umweltbedingungen Schritt halten können. Eine der größten Herausforderungen für die Evolutionsbiologie ist es daher derzeit, die Populationen zu identifizieren, welche vom Aussterben bedroht sind und gezielte Arterhaltungsprogramme benötigen – eine Herausforderung, welche von realistischeren und allgemeineren Modellen der genetischen Anpassung profitieren würde.

Das Ziel dieser Dissertation ist es daher, die kombinierten Effekte von gradueller Umweltänderung, stehender genetischer Variation sowie Pleiotropie für die genetische Basis der phänotypischen Anpassung zu untersuchen, um so einen ersten Schritt zu einem einheitlichen Modell der Anpassung zu machen, welcher sowohl die dem Selektionsprozess inhärente Dynamik, als auch die Komplexität realer Organismen berücksichtigt und überprüfbare Vorhersagen über kurz- und langfristige Evolution erlaubt.

Rapid evolution of quantitative traits: theoretical perspectives.

Im ersten Kapitel (publiziert; siehe Kopp und Matuszewski 2014) vergleiche ich verschiedene theoretische Modellierungsansätze, welche sich mit dem Potenzial zur genetischen Anpassung in sich verändernden Umwelten beschäftigen. Der Fokus dieses Übersichtsartikels liegt auf der Evolution quantitativer Merkmale (das heißt Merkmale, deren Werte auf einer kontinuierlichen Skala und durch eine große Anzahl von Loci definiert sind), welche von erheblicher stehender genetischer Varianz gekennzeichnet sind, und deren phänotypisches Optimum sich kontinuierlich mit der Zeit verändert. Besonderes Augenmerk gilt den sogenannten „kritischen Raten der Umweltänderung“ beziehungsweise den „maximal tragfähigen Raten genetischer Anpassung“. Dieses von Lynch und Lande (1993) und Bürger und Lynch (1995) eingeführte Konzept erlaubt es, unter Berücksichtigung populationsgenetischer Parameter, Raten zu berechnen, die – sollten sie überschritten werden – keinen langfristigen Populationserhalt erlauben. Obwohl dieser Ansatz in den letzten Jahren beispielsweise um multivariate Selektion (Gomulkiewicz

[2]“using [models] of instantaneous environmental change to understand adaptive evolutionary responses to gradual change will not only underestimate the amount of adaptation, but also predict the wrong genotypic and phenotypic changes”

und Houle 2009), räumliche Variation (Duputié et al. 2012) und phänotypische Plastizität kontinuierlich erweitert worden ist, blieb ein Hauptresultat bestehen: Maximal tragfähige Raten der genetischen Anpassung sind von der Größenordnung 0.1 *haldanes*, was einer Änderung des mittleren Phänotyps um 0.1 phänotypischen Standardabweichungen pro Generation entspricht. Allerdings zeigen Analysen, dass in natürlichen Populationen gemessene Raten nicht selten über den 0.1*haldanes* liegen (Hendry und Kinnison 1999; Gingerich 2009), jedoch die Mehrheit diesen Wert nicht überschreitet. Auf dieser Beobachtung beruhend kritisierten Barrett und Hendry (2012) kürzlich die aus der Theorie hergeleiteten kritischen Raten. Diese, so die Autoren, würden auf vielen unrealistischen Annahmen beruhen, wie beispielsweise dem „fortwährenden Populationserhalt in einer sich konstant ändernden Umwelt“[3], so dass „kritische Raten in natürlichen Populationen über Zeitspannen von konservationsbiologischen Interesse sehr unterschiedlich sein könnten.“[4]

Aufbauend auf dem Modell von Bürger und Lynch (1995) untersuche ich diese Einwände, indem ich sowohl kritische Raten der Umweltänderung als auch der genetischen Anpassung berechne. Dabei beschränke ich mich auf Zeitspannen von konservationsbiologischen Interesse – konkret 50 Generationen – und erlaube der Population temporär zu schrumpfen, wobei eine kritische Größe von 50 Individuen nicht unterschritten werden darf. Allerdings basieren meine Berechnungen auf einer deterministischen Approximation und vernachlässigen dementsprechend verschiedenste stochastische Einflüsse. Um zu quantifizieren, wie Raten phänotypischer Anpassung von nicht-selektiven Kräften, wie beispielsweise genetischem Drift, beeinflusst werden, habe ich das deterministische Modell zusätzlich durch individuen-basierte Simulationen komplementiert. Aufgrund dieser Modifikationen ist es allerdings nicht möglich, weiterhin ein dynamisches Gleichgewicht zwischen Umwelt- und evolutionärer Änderung anzunehmen, so dass kritische Raten der Umweltänderung nicht mehr formal equivalent zu maximalen Raten der genetischen Anpassung sind.

Tatsächlich zeigen meine Untersuchungen, dass kritische Raten der Umweltänderung über kürzere Zeiträume deutlich höher sein können als die von Bürger und Lynch (1995) vorhergesagten Raten. Maximal tragfähige Raten genetischer Anpassung hingegen – welche als Einzige in experimentellen Studien gemessen werden können – sind nahezu identisch und realtive Unterschiede zwischen kurz- und langfristigen evolutionären Raten übersteigen selten 30%. Allerdings sind diese Unterschiede zu vernachlässigen,

[3]“perpetual persistence under constant environmental change”
[4]“critical rates for natural populations over time frames of conservation interest could be very different”

betrachtet man die Unsicherheit der Schätzung der evolutionären Raten, die durch stochastische Fluktuationen verursacht werden. Meine Ergebnisse zeigen, dass, speziell in kleinen Populationen, genetischer Drift – selbst bei konstanten Umweltbedingungen – generationsweise Raten von bis zu 0.15 *haldanes* erzeugen und somit die von Bürger und Lynch (1995) vorhergesagte kritische Marke von 0.1 *haldanes* überschreiten kann. Zusammenfassend lassen diese Resultate erheblichen Zweifel an der Verwendung von evolutionären Raten zur Vorhersage und Identifikation von vom Aussterben bedrohten Populationen aufkommen.

Fisher's geometric model with a moving optimum.

Im zweiten Kapitel (publiziert; siehe Matuszewski et al. 2014a) richte ich nun den Fokus auf das „fundamentale Ereignis des genetischen Anpassungsprozesses" (Kopp und Hermisson 2009b)[5]: die Substitution eines ursprünglichen Alleles (das heißt einer Genvariante) durch eine vorteilhafte Mutation. Ein wichtiges Ziel, sowohl empirischer wie theoretischer Forschung, ist es, mehr über die statistischen Eigenschaften dieser Substitution zu lernen (Orr 2005b). In diesem Zusammenhang wurden kürzlich besondere Anstrengung unternommen, um die Verteilung der Effekte von sämtlichen Neumutationen (sowohl in Bezug auf deren phänotypischen als auch deren Fitnesseffekt; Martin und Lenormand 2006b; Eyre-Walker und Keightley 2007; Martin und Lenormand 2008) sowie die Verteilung der fixierten und somit zur genetischen Anpassung beitragenden Mutationen, genauer zu untersuchen (Gerrish und Lenski 1998; Orr 1998, 2002; Kopp und Hermisson 2009b; Mackay et al. 2009).

Das Hauptwerkzeug für das Studium der „Verteilung adaptiver Substitutionen" ist Fishers geometrisches Modell (FGM; Fisher 1930), welches den Anpassungprozess einer Population beschreibt, die als Folge einer plötzlichen Umweltänderung konstanter, stabilisierender Selektion ausgesetzt ist. Für dieses Szenario hat FGM drei Hauptvorhersagen aufgestellt, die zunehmend durch empirische Studien gestützt werden. Erstens entspricht die Verteilung der Fitnesseffekte von Neumutationen ungefähr einer (verschobenen) negativen Gammaverteilung (Martin und Lenormand 2006a; empirisch gestützt durch Hietpas et al. 2013). Zweitens ist die Verteilung adaptiver Substitutionen näherungsweise exponentiell, was bedeutet, dass die meisten fixierten Mutationen von kleinem und nur eine geringe Anzahl von großem Effekt sind (Orr 1998; empirisch gestützt durch Rockman 2012, aber siehe Bell 2009). Drittens nimmt der mittlere Effekt von fixierten Mutationen mit steigender organismischer Komplexität (das heißt mit der Anzahl der phänotypischen Merkmale) ab (Orr 2000; empirisch gestützt durch Cooper et al. 2007) – ein

[5]"the fundamental event during adaptation"

Phänomen, welches als die „Kosten der Komplexiät“[6] bezeichnet wird (Orr 2000; Welch und Waxman 2003; Wagner und Zhang 2011).

Im Gegensatz zu dem klassischen Fisher-Modell haben einige Studien ihren Fokus auf das sogenannte „moving-optimum“ Modell gerichtet, welches die Evolution eines quantitativen Merkmals unter stabilisierender Selektion beschreibt, dessen optimaler Phänotyp sich kontinuierlich mit der Zeit ändert (Lynch und Lande 1993; Bürger und Lynch 1995; Waxman und Peck 1999; Bürger und Gimelfarb 2002; Nunney 2003; Bello und Waxman 2006). Dadurch berücksichtigen diese Arbeiten, dass Umweltänderungen in der Natur genauso oft graduell wie auch plötzlich sind (Thompson 2005; Parmesan 2006; Perron et al. 2008) und tragen der seit Langem bekannten Notwendigkeit Rechnung, kontinuierliche Umweltänderungen in Modelle adaptiver Evolution zu integrieren (Maynard Smith 1976).

Die Eigenschaften individueller Substitutionen im „moving-optimum“ Modell wurden vor Kurzem genauer untersucht (Collins et al. 2007; Kopp und Hermisson 2007, 2009a,b). Diese Studien zeigten, dass Selektion für ein sich kontinuierlich bewegendes phänotypisches Optimum im Vergleich zu denen des Anpassungsprozesses unter konstanter Selektion (das heißt nach einer einzigen, plötzlichen Umweltänderung) fundamental verschiedene Charakteristiken aufweist. So ist die Verteilung der adaptiven Substitutionen unimodal (mit einem intermediären Modalwert) anstatt exponentiell, so dass die Mehrheit der Substitutionen von intermediärem, phänotypischem Effekt sind, während Substitutionen von kleinem und großem Effekt selten sind. Des Weiteren kann diese Verteilung vollständig durch einen einzigen Parameter beschrieben werden, welcher als skalierte Rate der Umweltänderung interpretiert werden kann und die genetischen sowie ökologischen Faktoren kombiniert und in Relation setzt.

Allerdings haben frühere Arbeiten zur genetischen Basis des Anpassungsprozesses im „moving-optimum“ Modell nur die Evolution eines einzigen phänotypischen Merkmals betrachtet (Collins et al. 2007; Kopp und Hermisson 2007, 2009a,b). Während diese Minimalmodelle wertvolle Einblicke über den Anpassungsprozess in sich kontinuierlich verändernden Umwelten lieferten, so wirkt Selektion in der Natur nicht auf einzelne Merkmale, sondern auf das gesamte Individuum. Diese Individuen besitzen in der Regel eine Vielzahl von Merkmalen, welche wiederum selbst von einer großen Zahl von Genen abhängen. Diese Gene können physisch auf dem selben Chromosom gekoppelt sein (Kopplung), sie können auf nicht-lineare Weise miteinander interagieren (Epistasie)

[6] “cost of complexity”

und zugleich mehrere Merkmale beeinflussen (Pleiotropie). Folglich findet der Anpassungsprozess in sehr komplexen und hochdimensionalen Genotyp- und Phänotypräumen statt.

Eine in diesem Kontext naheliegende Folgefragestellung ist, wie sich die Resultate des Ein-Merkmal-Modells verändern, wenn der Anpassungsprozess durch pleiotrope Korrelationen zwischen den phänotypischen Merkmalen unter Selektion beeinflusst wird. Um diese Frage zu beantworten, füge ich eines der Schlüsselmerkmale des FGM zum „moving-optimum“ Modell hinzu, nämlich den Effekt von phänotypischer Komplexität (beziehungsweise Pleiotropie, welches im Kontext von FGM äquivalent ist). Mit Hilfe analytischer Approximationen sowie individuen-basierter Simulationen untersuche ich, wie die erwartete Verteilung adaptiver Substitutionen von der Rate der Umweltänderung, der Anzahl der phänotypischen Merkmale (organismischer Komplexität) und von Selektions- und Mutationskorrelationen (das heißt von der Form der Fitnesslandschaft und der multivariaten Verteilung der Neumutationen) abhängt.

Übereinstimmend mit vorherigen Ein-Merkmals-Studien, zeigt meine Analyse des „moving-optimum“ Modells, dass die genetische Basis des Anpassungsprozesses kritisch von der Rate und der Art der Umweltänderung abhängt. Des Weiteren ist die Verteilung adaptiver Substitutionen zu einem Großteil durch einen einzelnen Parameter γ bestimmt, welcher die Rate der Umweltänderung mit dem Anpassungspotenzial der Population skaliert und so ein Kontinuum zwischen umwelt-limitierter und genetisch-limitierter Anpassung definiert (*sensu* Kopp und Hermisson 2009b). Im umwelt-limitierten Regime (das heißt, wenn sich die Umwelt nur sehr langsam ändert) kann die Population dem Optimum sehr dicht folgen, so dass die adaptiven Schritte klein sind und deren multivariate Verteilung die Fitnesslandschaft widerspiegelt. Im genetisch-limitierten Regime (das heißt, wenn sich die Umwelt sehr schnell ändert) fällt die Population weit hinter das Optimum zurück, so dass die adaptiven Schritte groß sind und deren Verteilung hauptsächlich von der Verteilung der Neumutationen bestimmt wird. Meine Resultate bestätigen und erweitern somit vorhergehende Studien adaptiver Evolution in sich verändernden Umwelten für einzelne phänotypische Merkmale (Collins et al. 2007; Kopp und Hermisson 2007, 2009a,b). Im Gegensatz zu den Vorhersagen für FGM (nach einer plötzlichen Umweltänderung) zeigen meine Resultate, dass die mittlere Effektgröße fixierter Mutationen mit dem Grad von Pleiotropie (das heißt organismischer Komplexität) zunimmt. Darüber hinaus scheint längerfristiger Populationsfortbestand nur im umwelt-limiterten Regime möglich – in dem der Anpassungsprozess von vielen kleinen adaptiven Schritten gekennzeichnet ist – dessen Parameterbereich in

komplexen Organismen jedoch zunehmend eingeschränkt wird. So nimmt die maximale Rate der Umweltänderung (Bürger und Lynch 1995, siehe oben) mit zunehmender organismischer Komplexität ab.

Catch me if you can: On the importance of standing genetic variation for the genetics of adaptation.

Wie die vorwiegende Mehrheit der Theorie des genetischen Anpassungsprozesses (Orr 2000, 2005a; Kopp und Hermisson 2009b; Matuszewski et al. 2014a) hat sich das zweite Kapitel dieser Dissertation auf genetische Anpassung von Neumutationen beschränkt. Wie bereits angemerkt, haben diese „adaptive-walk“ Modelle (Gillespie 1984; Kauffman und Levin 1987; Orr 2002, 2005b) über die Jahre viele robuste Vorhersagen geliefert (Orr 1998, 2000; Martin und Lenormand 2006a), welche von empirischen Studien gestützt werden (Cooper et al. 2007; Rockman 2012; Hietpas et al. 2013). Der Nachteil des Erfolges dieser Modelle ist allerdings, dass man in Bezug auf die genetische Basis des Anpassungsprozesses „kaum etwas über Adaptation durch bestehende genetische Variation sagen kann“[7] (Orr 2005b). Allerdings können auch quantitativ-genetische Modelle keine Antwort geben, da sie, gleichwohl sie bereits existierende stehende genetische Variation als die alleinige Quelle des genetischen Anpassungprozesses annehmen, nicht die Evolution einzelner Loci untersuchen.

Allein im letzten Jahrzehnt haben sich Populationsgenetiker ernsthafter mit dem genetischen Anpassungsprozess durch stehende genetische Variation und die Beschreibung der statistischen Eigenschaften individueller Allele beschäftigt (Orr und Betancourt 2001; Hermisson und Pennings 2005; Chevin und Hospital 2008). So berechneten Hermisson und Pennings (2005) die Wahrscheinlichkeit, dass ein Allel aus der stehenden genetischen Varianz in Folge einer plötzlichen Umweltänderung fixiert. Des Weiteren konnten sie zeigen, dass die Fixationswahrscheinlichkeit von Allelen der stehenden genetischen Varianz mit kleinem phänotypischen Effekt verglichen zu denen von Neumutationen erheblich erhöht ist. In ähnlicher Weise untersuchten Chevin und Hospital (2008) die Selektionsdynamiken an einem Fokallokus in Gegenwart von stehender genetischer Hintergrundvarianz und fanden heraus, dass diese die Alleltrajektorie am Fokallokus erheblich beeinflusst. Eine ähnliche Beobachtung machten Lang et al. (2011), welche experimentelle Evolution in Hefe durchführten. Darin untersuchten sie das Schicksal mehrerer vorteilhafter Mutationen in hunderten von Populationen. Sie konnten zeigen, dass der selektive Vorteil einer einzelnen Mutation nur eine kleine Rolle für deren evolutionäres Schicksal spielt. Weitaus wichtiger und von zentraler Bedeutung ist stattdessen

[7] “we cannot say anything about adaptation from standing genetic variation”

der genetische Hintergrund auf dem die Mutation auftritt, welcher nicht notwendigerweise prä-existent sein muss, sondern ebenso schnell durch viele Neumutationen generiert werden kann. Nichtsdestotrotz sind die meisten Vorhersagen bezüglich des genetischen Anpassungsprozesses von stehender genetischer Variation nur verbaler Natur und besagen, dass „im Vergleich zu Neumutationen, Adaptation von stehender genetischer Varianz wahrscheinlich schneller und vermehrt durch Fixation von Allelen mit kleinem phänotypischem Effekt voranschreitet [...]“[8] (Barrett und Schluter 2008). Trotz dieser Fortschritte bleibt eine der zentralen Fragen immer noch unbeantwortet: Welche von der Vielzahl der in einer Population segregierenden stehenden Varianten können am Ende fixieren und zum genetischen Anpassungprozess beitragen und wie unterscheidet sich deren phänotypische Effektgrößenverteilung von der von Neumutationen?

Das Ziel des dritten Kapitels meiner Dissertation (in Vorbereitung; siehe Matuszewski et al. 2014b) ist es, dazu beizutragen, diese „offensichtlichste theoretische Limitierung den genetischen Anpassungsprozess betreffend“[9] (Orr 2005b) zu überwinden, und die ökologischen und genetischen Faktoren zu untersuchen, welche gemeinsam die Basis des genetischen Anpassungsprozesses von stehender genetischer Variation definieren. Mittels analytischer Approximationen leite ich die Verteilung der stehenden adaptiven Substitutionen her und diskutiere deren Abhängigkeit von der effektiven Populationsgröße, der Stärke der Selektion sowie ökologischen Faktoren.

In Übereinstimmung mit Barrett und Schluter (2008) finde ich heraus, dass, im Vergleich zu Neumutationen, der Anpassungprozess durch stehende genetische Variation von kleineren „Schritten“ gekennzeichnet ist. Meine Analyse zeigt, dass die genetische Basis des Anpassungsprozesses von stehender genetischer Varianz entscheidend von der Effizienz der Selektion – welche wiederum von der Populationgröße, der Stärke der (stabilisierenden) Selektio und der Rate der Umweltänderung definiert wird – abhängt. Im Gegensatz zu Studien, die Adaptation ausschließlich auf Neumutationen beschränken (Perron et al. 2008; Bell und Gonzalez 2011; Lindsey et al. 2013; Bell 2013), zeigen meine Resultate, dass Populationen, deren Evolution nur auf stehender genetische Varianz beruht, besser angepasst sind und weitere phänotypische Distanzen zurücklegen können, wenn sich die Umwelt schnell ändert.

[8] “compared with new mutations, adaptation from standing genetic variation is likely to lead to faster evolution [and] the fixation of more alleles of small effect [...]”
[9] “the most obvious theoretical limitation when describing the adaptive process”

Synopsis und Ausblick.

> "When a species is well adapted to the conditions which environ it, it flourishes; when imperfectly adapted it decays; when ill-adapted it becomes extinct."
>
> — Alfred Russel Wallace, *Contributions to the theory of natural selection*

Gemessen in evolutionärer Zeit haben wir in weniger als einem Augenblick, ausgehend von Charles Darwin und Alfred Russel Wallace, welche mit ihrer Beschreibung des „Kampfes ums Überleben“[10] und der Ursachen natürlicher Selektion den Grundstein für die heutige Evolutionsbiologie gelegt haben, das Zeitalter von „Transcriptomics“, „Proteomics“ und „Whole-Genome Sequencing“ erreicht, welche uns erlauben, Evolution in natürlichen Populationen in Echtzeit zu beobachten (Hendry und Kinnison 1999; Collins et al. 2007; Lindsey et al. 2013). Dieser technische Fortschritt hat jedoch dazu geführt, dass einer immer weiter zunehmenden Menge an Daten eine immer größer werdende Lücke zur Theorie gegenübersteht. Das Ziel dieser Dissertation ist es, unser Verständnis des genetischen Anpassungsprozesses voranzutreiben und Modelle zu entwickeln, welche, durch die explizite Berücksichtigung von genetischen und ökologischen Faktoren sowie stehender genetischer Variation, der Dynamik des Selektionsprozesses Rechnung tragen.

Alle Kapitel dieser Dissertation betonen die Wichtigkeit der Dynamik der selektiven Umwelt für den genetischen Anpassungprozess und unterstreichen, dass die genetische Basis des Anpassungsprozesses in kritischer Weise vom Tempo und der Art der Umweltänderung abhängt. So sind im umweltlimitierten Regime – in dem sich die Umwelt nur sehr langsam ändert und das langfristige Überleben einer Population am wahrscheinlichsten ist (siehe auch vergleichbare empirische Studien Perron et al. 2008; Bell und Gonzalez 2011; Lindsey et al. 2013) – ökologische Faktoren wichtiger als genetische. Im Gegensatz dazu zeigen meine Untersuchungen des „moving-optimum“ Modells, dass sich die genetische Basis des Anpassungsprozesses von stehender genetischer Variation stark zu der von Neumutationen unterscheidet. So ist der Anpassungsprozess von stehender genetischer Variation durch viele kleine Schritte und nur wenige große gekennzeichnet. Außerdem sind Populationen, deren Evolution nur auf stehender genetische Varianz beruht, besser angepasst und haben eine höhere Überlebenschance, wenn sich die Umwelt schnell ändert. Allerdings ist die Vorhersage und Identifikation von vom Aussterben bedrohten Populationen, basierend auf „maximalen evolutionären Raten“ , schwierig, da

[10] “struggle for existence”

genetischer Drift sowie Samplingeffekte bereits in untragbar hohen „evolutionären Raten“ resultieren können – selbst in Fällen, in denen sich die Umwelt überhaupt nicht ändert.

Darüber hinaus gibt es ein paar Entwicklungsgebiete, welche die Basismodelle – wie beispielswiese die in dieser Dissertation präsentierten Modelle – noch realistischer machen können. Natürliche Populationen leben in fragmentierten Umwelten und können zusätzlich zu genetischer Anpassung auch durch Migration (Pease et al. 1989; Kirkpatrick und Barton 1997; Polechová et al. 2009; Schloss et al. 2012; Duputié et al. 2012; Boeye et al. 2013) und durch phänotypische Plastizität (Chevin et al. 2010; Reed et al. 2010; Chevin et al. 2012; Gienapp et al. 2013) auf Änderungen in ihrer Umwelt reagieren. In der Tat ist die Rolle von phänotypischer Plastizität für den Anpassungsprozess gut dokumentiert (Ghalambor et al. 2007; Hendry et al. 2008; Pfennig et al. 2010; Merilä 2012) und theoretische Modelle zeigen, dass Plastiziät die Annäherung an ein neues phänotypisches Optimum unterstützt (Lande 2009) und so das Risiko des Aussterbens verringert (Chevin und Lande 2010). Der Effekt von Plastizität hängt allerdings von der Verlässlichkeit des Umweltreizes (Reed et al. 2010) sowie deren Erhaltungskosten ab (wenn die Population perfekt angepasst ist; Chevin et al. 2010). Studien, welche phänotypische Plastizität mit explizit genetischen Modellen verbinden, sind selten (Draghi und Whitlock 2012) und es existieren derzeit keine multivariaten Plastizitätsmodelle, die Anpassung an sich verändernde Umwelten betrachten. Hier könnten meine Modelle als Ausgangspunkt für vertiefende Studien der Interaktionen zwischen phänotypischer Plastizität und genetischer Anpassung dienen.

Ebenso wie der Effekt von phänotypischer Plastizität ist der von Migration stark vom Kontext abhängig. Während Genfluss von schlecht-angepassten Populationen den Anpassungsprozess behindern kann, kann Genfluss ebenso die Überlebenschancen von Populationen erhöhen, indem er die Erschließung von größeren geographischen Gebieten und die Verbreitung von vorteilhaften Allelen ermöglicht (Schiffers et al. 2013). Andere Studien untersuchten den Anpassungsprozess bei einem sich änderenden Umweltgradienten, das heißt zu einem phänotypischen Optimum, welches sich sowohl in Zeit als auch im Raum, ändert (Pease et al. 1989; Kirkpatrick und Barton 1997; Polechová et al. 2009; Duputié et al. 2012). Allerdings war der Fokus dieser Untersuchungen auf den Populationserhalt und nicht auf die Art, Effektgröße und den Ursprung von Mutationen, die zur lokalen Anpassung beitragen, gerichtet. Des Weiteren gibt es derzeit keine Studien, die den gemeinsamen Effekt von Plastizität und genetischer Anpassung in einem explizit räumlich-strukturierten Modell bei kontiniuerlicher Umweltänderung untersucht.

In der Natur evolvieren Populationen nicht in Isolation, sondern sind in ein Netzwerk von ökologischen Interaktionen eingebettet, so dass Vorhersagen zum Anpassungsprozess in sich verändernden Umwelten unter Berücksichtigung dieser Interaktionen gemacht werden sollten. Studien haben gezeigt, dass interspezifische Konkurrenz sowohl positive als auch negative Effekte auf den genetischen Anpassungsprozess haben kann. Während die Anwesenheit eines Konkurrenten die Populationsgröße einer fokalen Spezies reduzieren und den Zugang zu neuen ökologischen Nischen blockieren kann (Johansson 2007; Jones 2008; Jones und Gomulkiewicz 2012; Osmond und Mazancourt 2013; Uecker und Hermisson 2014), kann Konkurrenz auch den genetischen Anpassungsprozess beschleunigen, falls ein Konkurrent (oder Räuber) eine fokale Spezies in die Richtung des neuen Optimums „drängt“ (Jones 2008; Osmond und Mazancourt 2013; Uecker und Hermisson 2014). Die Effekte von Interaktionen zwischen verschiedenen Spezies auf den genetischen Anpassungsprozess sind allerdings bisher nicht untersucht worden.

Zusammen mit den Studien experimenteller Evolution in sich kontinuierlich verändernden Umwelten (Collins 2004; Perron et al. 2008; Lindsey et al. 2013) verspricht die Integration dieser Ansätze, heutige Modelle noch stärker an die in der Natur ablaufenden Prozesse anzulehnen, und so unser Verständnis des Adaptationsprozesses verschiedener Spezies in ihrem fortlaufendem „Kampf ums Überleben“[11] (Darwin 1859) zu erweitern.

[11]“struggle for existence”

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Epilog

"Begin at the beginning," the King said gravely, "and go on till you come to the end: then stop."

— Lewis Carroll, Alice in Wonderland