Multivariate selection and the making and breaking of mutational pleiotropy

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Abstract

The role of mutations have been subject to many controversies since the formation of the Modern Synthesis of evolution in the early 1940ties. Geneticists in the early half of the twentieth century tended to view mutations as a limiting factor in evolutionary change. In contrast, natural selection was largely viewed as a “sieve” whose main role was to sort out the unfit but which could not create anything novel alone. This view gradually changed with the development of mathematical population genetics theory, increased appreciation of standing genetic variation and the discovery of more complex forms of selection, including balancing selection. Short-term evolutionary responses to selection are mainly influenced by standing genetic variation, and are predictable to some degree using information about the genetic variance–covariance matrix (G) and the strength and form of selection (e.g. the vector of selection gradients, β). However, predicting long-term evolution is more challenging, and requires information about the nature and supply of novel mutations, summarized by the mutational variance–covariance matrix (M). Recently, there has been increased attention to the role of mutations in general and M in particular. Some evolutionary biologists argue that evolution is largely mutation-driven and claim that mutation bias frequently results in mutation-biased adaptation. Strong similarities between G and M have also raised questions about the non-randomness of mutations. Moreover, novel mutations are typically not isotropic in their phenotypic effects and mutational pleiotropy is common. Here I discuss the evolutionary origin and consequences of mutational pleiotropy and how multivariate selection directly shapes G and indirectly M through changed epistatic relationships. I illustrate these ideas by reviewing recent literature and models about correlational selection, evolution of G and M, sexual selection and the fitness consequences of sexual antagonism.

Keywords Correlational selection · G-matrix · M-matrix · Mutation bias · Quantitative genetics · Pleiotropic mutations
Introduction

Mutations provide novel genetic variation to populations, alongside with recombination, and the mutational process is necessary for sustained long-term evolutionary change. The mutational process was one of the key evolutionary processes that were formalized by the mathematical population geneticists Fisher, Haldane and Wright (Provine 1971, 1986; Lynch 2007; Svensson and Berger 2019). Mathematical population genetics in turn provided the conceptual and theoretical foundation for the later establishment of the Modern Synthesis (MS) or the Evolutionary Synthesis (Mayr and Provine 1998; Svensson 2022).

From the early days of the MS and up to the present, the random nature of mutations and the role of mutations in evolution has generated controversy. The architects of the MS, including Dobzhansky, Mayr and Huxley, argued that mutations were random with respect to organism’s current needs and mutations were not directed in terms of their functions and fitness effects (Mayr and Provine 1998). By “random” it was never meant that mutation rates were not influenced various external and internal factors, such as temperature, radiation and mutagens, which no biologist would deny, neither today nor in the early days of the MS (Luria and Delbrück 1943; Lederberg and Lederberg 1952; Mayr and Provine 1998; Galhardo et al. 2007; Berger et al. 2021). Neither did random mean that mutation rates are equal across the genome (Svensson and Berger 2019). On the contrary, both mutation rates and the fitness effects of mutations differ between loci (Martincorena et al. 2012; Svensson and Berger 2019; Monroe et al. 2022). Recent work on the plant Arabidopsis thaliana, for instance, has revealed that mutation rates are influenced GC content, histone modifications, and chromatin accessibility and that coding region mutation rates are lower in genes where mutations are more likely to be deleterious (Weng et al. 2019; Monroe et al. 2022). The relative importance of structural constraints vs. selection in reducing mutation rates and in explaining intragenomic variation in mutation rates is subject to discussion and ongoing research (Martincorena et al. 2012; Svensson and Berger 2019; Monroe et al. 2022). Regardless of the causes of such intragenomic variation in mutation rates, the result is mutation bias, where some loci contribute more in providing mutational input to the population than other loci (Yampolsky and Stoltzfus 2001; Stoltzfus and Yampolsky 2009; Stoltzfus and McCandlish 2017). Population geneticists have argued that overall genomic mutation rates can evolve by natural selection to become lower, although this is less likely to happen in small populations where selection is weak relative to genetic drift (Lynch 2010). Regardless, the evolutionary origin of mutation bias (i. e., selection versus structural constraints) is somewhat controversial if we focus on single loci (Monroe et al. 2022). It is uncontroversial that overall genomic mutation rates can evolve by natural selection, within the constraints set by genetically effective population size (N_e) and genetic drift (Galhardo et al. 2007; Baer et al. 2007; Lynch 2010).

The population geneticists J. B. S. Haldane and R. A. Fisher both concluded that mutation rates were too weak in themselves to result in directional evolution, compared to the stronger effects of natural selection (Haldane 1927, 1932, 1933; Fisher 1930). The result was the so-called “opposing pressure” view of evolution, or mutation-selection balance, where most mutations were thought to be deleterious and were assumed to be opposed by selection, and where populations reach a dynamic equilibrium between these two evolutionary forces. By and large, this classical view of the evolutionary process have largely been upheld by later research in population and molecular evolutionary genetics. Neither mutation supply (overall genomic mutation rate across all loci) nor mutation bias (differences between loci in mutation rates) alone will result in directional evolutionary change,
unless population sizes are small and the effects of genetic drift is strong, mutation rates are high, selection is weak or certain criteria such as reciprocal sign epistasis for fitness are fulfilled (Lynch 2007; Svensson and Berger 2019). In contrast, in neutral evolution at the molecular level (where selection per definition is absent), it is uncontroversial that mutation bias can and does often lead to evolutionary directionality, as loci with the highest mutation rates will evolve faster than loci with lower mutation rates, all else being equal (Sueoka 1988; Weng et al. 2019; Monroe et al. 2022).

Nevertheless, the randomness of mutations have repeatedly been questioned since the formation of the MS. Some biologists have argued that mutations are not random but directed (Noble 2013, 2015, 2017, 2021) or that adaptive evolution is mutation-driven rather than primarily governed by natural selection (Nei 2013). Moreover, the generally accepted framework of evolutionary change as resulting from random mutations acted upon by selection has been claimed to be insufficient by some radical critics of the MS (Ho and Saunders 1979; Shapiro 2011). By and large, these claims have been firmly dismissed, on both theoretical and empirical grounds (Charlesworth et al. 1982, 2017; Futuyma 2017).

To date, there is no convincing empirical evidence that directed mutations are important or that mutation rates alone have a strong influence on adaptive evolution, although mutation bias clearly play a role in neutral evolution at the molecular level (Sueoka 1988; Lenski and Mittler 1993; Sniegowski and Lenski 1995; Gardner 2013; Futuyma 2017; Svensson and Berger 2019). Directed mutations are here defined as an increased frequency of beneficial mutations in response to an environmental change, that is, a potential mechanism by which organisms would be able to increase the rate of input of adaptive mutations and thus facilitate natural selection, for which there is no experimental and empirical evidence, at least not among any Metazoan organisms (Lenski and Mittler 1993; Futuyma 2017; Svensson and Berger 2019). Note that the fact that mutation rates are not entirely random but are affected by various external and environmental factors and vary across the genome (see above) is not evidence for directed mutations, which are strictly defined in terms of the organism’s current needs, with an expected excess frequency of beneficial mutations following an environmental change (Svensson and Berger 2019). Moreover, Fisher’s Geometric Model (FGM) (Fisher 1930) predicts a higher absolute number (although not a higher frequency) of beneficial mutations when populations are far away from their adaptive peaks, such as in stressful or novel environments (Svensson and Berger 2019). Fisher’s model is largely congruent with laboratory experiments and field studies on mutation accumulation (MA) lines, which have showed that mutation rates, fitness effects of novel mutations and mutational variances are highly context- and environment-dependent, and that fitness-effects of mutations are often larger in more stressful environments (Galhardo et al. 2007; Rutter et al. 2010; MacLean et al. 2013; Weng et al. 2021) An emerging view is therefore that evolution is not solely driven by the deterministic fitness-enhancing force of natural selection (Svensson and Berger 2019). Evolutionary biology today therefore recognizes historical contingencies such as the arrival order of mutations and mutational history (Losos et al. 1998; Huey et al. 2000; Svensson and Berger 2019), as exemplified in models of “mutation-order speciation” (Schluter 2009; Mendelson et al. 2014).

Empirical evidence, however, has accumulated that seemingly challenges the supposedly random nature of mutations. Upon closer inspection such new empirical evidence is fully compatible with the traditional view that mutations are not directed. Such new empirical evidence include stress-induced mutations in microbes that enhances fitness in stressful environments (Galhardo et al. 2007; Baer et al. 2007; Lamm 2014), mutations that seemingly predict long-term phenotypic evolution in Drosophila (Houle et al. 2017) and quantitative-genetic models that predict close alignment between mutational variation, standing
genetic variation and the selective surface (Jones et al. 2014; Svensson et al. 2021). Here I discuss these challenges and the role of the mutational process in generating historical contingencies and in shaping genetic architectures, sex differences, sexual selection and sexual conflict.

The random nature of the mutational process

To what extent do varying mutation rates across the genome arise because of structural constraints or because of selection for lower mutation rates in certain regions (e.g., in essential housekeeping genes; see Martincorena et al. 2012; MacLean et al. 2013; Monroe et al. 2022)? The answer to this question is likely to vary between genes, genomes and organisms (Svensson and Berger 2019). A selectionist account would interpret lower mutation rates in certain genomic regions as an adaptive evolutionary outcome to avoid the costly fitness effects of deleterious mutations that disrupt essential gene functions (Monroe et al. 2022). A neutralist account would emphasize the essential role of effective population size ($N_e$) and would point to the fact that selection for reduced mutation rates is more efficient when selection outpowers genetic drift, such as in extremely large microbial populations (Lynch 2010). A structuralist account would emphasize physical properties such as DNA fragility and genome instability (Aguilera and Gómez-González 2008; Lamm 2014), that make certain genomic regions more vulnerable to disruption, e.g., by increasing double-strand breaks and deletions (Xie et al. 2019). These explanations for differences in mutation rates within or between genomes and organisms are certainly not mutually exclusive.

Regardless of their relative importance, these mechanisms will generate mutation bias across the genome, meaning that mutation rates will be higher in certain genomic regions compared to others (Lamm 2014; Svensson and Berger 2019). The evolutionary importance of such mutation bias in adaptive evolution is subject to some controversy. Some researchers argue that mutation bias often generates mutation-biased adaptation and that it can explain a significant fraction of parallel evolution, can lead to non-random long-term evolutionary trends and that mutation rates can influence fixation rates (Yampolsky and Stoltzfus 2001; Stoltzfus 2006; Stoltzfus and Yampolsky 2009; Stoltzfus and Cable 2014; Stoltzfus and McCandlish 2017; Gomez et al. 2020). Other researchers instead emphasize that mutation bias is unlikely to overpower selection, unless mutation rates are high, selection is weak, standing genetic variation is limited or certain conditions like reciprocal sign epistasis for fitness are fulfilled (Svensson and Berger 2019). Regardless, the existence of mutation bias is not in doubt, but its underlying causes (i.e., adaptive, neutral or structural explanations) and evolutionary consequences is subject to discussion.

Mutation rates are certainly not random with respect to the physical environment either (Svensson and Berger 2019). Environmental factors like radiation, chemical reagents and temperature can directly influence mutation rates by elevating them or indirectly generate environmental stress during which natural or sexual selection against deleterious mutations becomes stronger (Berger et al. 2017, 2021; Baur and Berger 2020). Mutation rates also vary between different biogeographic regions with different temperatures and climatic regimes, such as between the tropics and temperate areas (Brown 2014). In asexual microbes, genome-wide mutation rates increase under stressful conditions, which has been interpreted as an adaptive strategy (Galhardo et al. 2007; Martincorena et al. 2012; Lamm 2014). The rationale for such an adaptive argument is that even though the frequency of beneficial mutations will not increase under
stressful conditions the absolute number of beneficial mutations will increase when overall genomic mutation rate increases and when populations are further away from their adaptive peaks (Svensson and Berger 2019). In asexual populations inhabiting stressful environments, genotypes with high mutation rates can therefore spread more easily because tight linkage disequilibrium enable such “mutator” genotypes to hitch-hike with novel beneficial mutations (Galhardo et al. 2007; Baer et al. 2007). Once the population has reached its fitness peak, however, the fitness benefits of mutators will gradually disappear, and in well-adapted populations the vast majority of novel mutations—even if random—will decrease fitness and displace the population from the optimum (Svensson and Berger 2019; Connallon and Hodgins 2021). Hence, when a population is near its fitness peaks, mutation rates are expected to decrease due to natural selection, although the efficiency of selection will depend on the genetically effective population size ($N_e$) and the resulting genetic drift (Baer et al. 2007; Lynch 2010). In summary; there is clear empirical evidence that genome-wide mutation rates can evolve, especially in asexual microbes and in organisms with large effective population sizes (Baer et al. 2007). However, the majority of novel mutations are thought to be neutral or slightly deleterious with respect to fitness and the fraction of advantageous mutations are typically less than 10% of non-neutral mutations (Eyre-Walker and Keightley 2007). The frequency of beneficial mutations varies between different organisms and populations and is subject to ongoing empirical research (Rutter et al. 2010; Weng et al. 2019, 2021). There is no evidence for directed or adaptive mutations that arise at higher frequencies in response to organism’s current needs. These basic insights from evolutionary and genomic research contrast with the claims by some critics of evolutionary theory who argue that mutations are non-randomly biased in purposeful directions (Noble 2013, 2015, 2017, 2021). Clearly, and with respect to fitness, novel mutations are random in the sense that they do not systematically improve organismal performance (Galhardo et al. 2007; Baer et al. 2007).

In the short term, non-neutral mutations tend to reduce mean population fitness because the majority are slightly or largely deleterious (Lynch et al. 1995), although this is disputed by some (Rutter et al. 2010; Weng et al. 2021; Monroe et al. 2022). Given that most mutations which affect fitness are deleterious, the mutational process therefore largely counteracts the fitness-enhancing force of selection which is the only known evolutionary process that can systematically increase fitness across generations (Svensson 2022). Therefore, in adaptive evolution and with respect to fitness, mutationists who downplay selection and who claim that evolution is mutation-driven (Nei 2013) are clearly wrong. A more nuanced view is instead that adaptive evolution is sometimes mutation-limited, conditions which might be fulfilled in large asexual populations of microbes and possibly also in some Metazoan organisms (McCandlish and Stoltzfus 2014; Houle et al. 2017). Few evolutionary biologists deny that neutral evolution at the molecular level is largely driven by mutations, that genomic mutation rates can evolve and that mutation bias exists. Mutation and mutation bias can therefore influence both trajectories and evolutionary outcomes in combination with selection and genetic drift (Svensson and Berger 2019; Svensson 2022). The issue is whether these acknowledged aspects about the mutational process necessitate a major revision of evolutionary theory or vindicate old ideas about mutationism, internalism or orthogenesis that were discredited after the establishment of the MS (Svensson 2022). Here, and elsewhere (Svensson and Berger 2019; Svensson 2022) I have argued that neither the fact that mutation rates can evolve or that mutation bias exist and can influence evolutionary outcomes necessitates any major revision of the current evolutionary
theoretical framework, although other authors might disagree (Stoltzfus 2006; Stoltzfus and Cable 2014; Gomez et al. 2020).

**Mutation bias, mutation-biased adaptation, mutation order and mutation supply**

Population genetic models of how mutation bias can lead to mutation-biased adaptation are often two-locus models (Yampolsky and Stoltzfus 2001; Gomez et al. 2020). Such models make several implicit or explicit assumptions about linkage disequilibrium, reciprocal sign epistasis for fitness, that selection is weak relative to beneficial mutation rates, that gene flow is low and that the amount of standing genetic variation and extent of clonal interference is limited and/or genetically effective population sizes are small (Yampolsky and Stoltzfus 2001; Lynch 2007; Stoltzfus and Yampolsky 2009; McCandlish and Stoltzfus 2014; Svensson and Berger 2019; Gomez et al. 2020; Soares et al. 2021). These population genetic models are useful, as they show what is possible, provided, that the model assumptions are fulfilled. It then becomes an empirical question to what extent and how often these assumptions are fulfilled in natural populations. For instance, one biological scenario where mutation bias could play an important role are in mutation-limited and large populations, with little standing genetic variation and with low clonal interference (McCandlish and Stoltzfus 2014). Under such circumstances, novel beneficial mutations will quickly sweep to fixation shortly after their origin, as captured by so-called “origin-fixation”-models (McCandlish and Stoltzfus 2014). These models are useful, as they reveal both the circumstances during which mutation bias could play an important role, i. e., when mutation rates can influence fixation rates, but also the conditions when these assumptions are met. Mutation bias can play some role when populations are mutation-limited, when selection coefficients are small and when the amount of standing genetic variation is low (McCandlish and Stoltzfus 2014; Soares et al. 2021). If these assumptions in origin-fixation models are violated, e. g. selection coefficients are large, beneficial mutation rates are low and/or standing genetic variation is large, mutation bias is unlikely to play a major role in adaptive evolution (McCandlish and Stoltzfus 2014; Svensson and Berger 2019; Soares et al. 2021). Some biologists argue that these assumptions are not as restrictive as has been hitherto assumed and insist that mutation bias is likely to be prevalent in natural populations (Gomez et al. 2020). I agree with McCandlish and Stoltzfus (2014) that the biological assumptions in origin-fixation models should not be taken for granted, but it is entirely an empirical issue how often these assumptions are fulfilled in natural populations. These conditions might sometimes be fulfilled in populations of asexual microbes, where selection is strong and when novel beneficial mutations enter a mutation-limited population with low amount of standing genetic variation and with little clonal interference (McCandlish and Stoltzfus 2014). In contrast, when standing genetic variation is abundant, and unless there is strong reciprocal sign epistasis for fitness or mutation rates are high, mutation bias will play a less important role (Svensson and Berger 2019). Given immense empirical evidence for abundant standing genetic variation in natural populations (Barrett and Schluter 2008), that selection is typically strong in nature (Kingsolver et al. 2001; Svensson et al. 2006; Siepielski et al. 2017) and that mutation rates are low (Haldane 1927, 1933; Fisher 1930; Svensson and Berger 2019), the conditions for mutation bias to play
a major role in adaptive evolution are rather restrictive, although by no means impos-
sible (Gomez et al. 2020).

Proponents of mutation-biased adaptation might have somewhat exaggerated its impor-
tance and downplayed the rather restrictive conditions under which we can expect to see it (Yampolsky and Stoltzfus 2001; Stoltzfus 2006; Stoltzfus and Yampolsky 2009; Stoltzfus and Cable 2014; Gomez et al. 2020). In a nuanced review these restrictive assumptions of origin-fixation models were critically discussed (McCandlish and Stoltzfus 2014). The authors emphasized that the assumptions of origin-fixation models should not be taken for granted but should be treated as hypotheses in need of empirical tests (McCandlish and Stoltzfus 2014). Such a nuanced view is welcome, as these models are especially permissive for mutation-biased adaptation and might therefore give the impression that mutation-
biased adaptation is more common than the empirical evidence actually suggest.

Models of mutation-biased adaptation often assume a few loci, asexuality and/or strong linkage disequilibrium, low amounts of standing genetic variation and mutation-limited populations (Yampolsky and Stoltzfus 2001; Svensson and Berger 2019; Gomez et al. 2020; Soares et al. 2021). However, many evolutionary biologists are interested in poly-
genic traits, but I am not aware of any quantitative genetic models of mutation-biased adap-
tation. Nevertheless, when many loci influence a quantitative character (e. g., body size) and the contribution from each locus is small (i. e., the infinitesimal model; (Lande 1976)), one could easily imagine a many-to-one mapping from genotype to phenotype (Fig. 1). In other
words, multiple genotypes can result in the same phenotype, even if everything else 
stays the same, e. g. populations reside in identical environments and experience identical selection pressures towards a fitness optimum (Fig. 1). Then, assuming that populations are subject to stabilizing selection around a shared fitness optimum, mutation bias could play a role as the arrival order of new mutations at different loci can create historical contingen-
cies in the local genetic architectures (Fig. 1). A mutation that increases the trait value at 
one locus will also indirectly generate selection for mutations that decrease the trait value at another locus, so that the optimum phenotype remains, which is a form epistasis for fitness (Fig. 1). Each population will then experience a unique mutational history, where there might be a role for “arrival of the fittest”. That is, the stochastic nature of the muta-
tional process will ensure that populations will become genetically divergent even if they would remain phenotypically identical (Fig. 1). This simple graphical model shows that there is indeed a potential for mutation bias at the level of underlying genetic architectures, even though at the phenotypic level it is selection that maintains similar phenotypes or drives parallel evolution (Fig. 1).

A potential empirical example of mutation-biased adaption for a quantitative phenotypic 
traits is the parallel evolution of geographic wing length clines in Drosophila subob-
scura in Europe and in its introduced range in North America (Huey et al. 2000). Flies 
on both continents evolved highly parallel wing size clines, with populations at higher 
latitudes having longer wings (Huey et al. 2000). However, the parallelism at the pheno-
typic level was caused by different parts of the wing becoming extended in Europe and 
North America, respectively, implying historical contingency in terms of which mutations 
that were fixed on the two continents (Huey et al. 2000). Apparently, there exist multiple 
genetic “solutions” to the same ecological “problem”, i. e., to evolve larger wings at higher 
latitudes (Huey et al. 2000). This might be a potential empirical examples of how mutation 
bias in a quantitative character can influence the evolutionary outcome and shape parallel 
evolution at the phenotypic level, although it should be underscored that this evolutionary 
change could have been caused by selection on standing genetic variation and there is no
Recent genomic studies have revealed the role of loss-and-function mutations in generating parallel phenotypic evolution of complex quantitative traits (Xie et al. 2019; Fulgione et al. 2022). One such example are the repeated freshwater colonizations of stickleback fish (*Gasterosteus aculeatus*) and subsequent parallel adaptive phenotypic evolution to this novel environment (Xie et al. 2019). The repeated pelvic losses in these freshwater stickleback populations are caused by recurrent deletions of a pelvic enhancer of the *Pitx1* gene which increase double-strand breaks and deletions (Xie et al. 2019). Elevated mutation rate at this locus depends on DNA replication direction and is caused by TGG-dinucleotide repeats, resulting in increased DNA fragility (Xie et al. 2019). It is important to underscore that parallel adaptation to the novel freshwater is driven by natural selection, not by mutations which mainly serves a dispositional role to selection in this scenario, facilitating “arrival of the fitness” (sensu (Wagner 2015)). The mutations therefore
created novel loss-of-function genotypes and phenotypes that by coincidence turned out to become adaptive in their novel environments (Xie et al. 2019). The elevated mutation rate in the Pitx1 gene makes the adaptive evolution more predictable also at the genomic level, and not only at the phenotypic level. However, given that there are many ways to generate loss-of-function genotypes and phenotypes, this and similar cases of parallel phenotypic evolution (Fulgione et al. 2022) might therefore more exemplify the predictability of natural selection in novel environments and many-to-one-mapping of fitness, rather than demonstrating any creative role of mutation bias. When mutation supply is high and there are many mutations occurring every generation, the balance between selection and mutation is tipped towards the former, meaning that the mutation with the highest selection coefficient will fix in the population (Wortel et al. 2021). It is therefore important to emphasize that mutation bias does not independently cause the fixation biases in these novel environments (Xie et al. 2019; Fulgione et al. 2022), but it is selection which is the main driver of their parallel evolution (Svensson and Berger 2019).

Stochasticity and historical contingency in evolution

My discussion above about the role of mutation supply and mutation bias in adaptive evolution and in parallel evolution, highlights both the deterministic role of natural selection in evolution, as well as important roles for stochasticity (Lenormand et al. 2009) and historical contingencies (Losos et al. 1998; Huey et al. 2000; Svensson 2022). A major goal of much evolutionary biology research is to understand and quantify the relative importance of deterministic and stochastic factors in affecting phenotypic outcomes on both micro- and macroevolutionary time scales (Losos et al. 1998; Huey et al. 2000; Eroukhmanoff et al. 2009). Thus, modern evolutionary biology research is far away from the panadaptationist position in some research traditions, where the optimizing role of selection is sometimes overemphasized, particularly behavioural ecology (Lewens 2019). At the other extreme, some proponents of mutation-biased adaptation have overplayed the mutational process’ role in generating fixation biases, sometimes claiming it to be of almost equal importance as natural selection in adaptive evolution (Yampolsky and Stoltzfus 2001; Stoltzfus 2006; Stoltzfus and Yampolsky 2009; Stoltzfus and Cable 2014). Empirical data and an extensive body of theoretical work in population genetics and evolutionary biology do not, however, support either of these two rather extreme positions, i.e., neither panadaptationism nor Mendelian-mutationism (Svensson 2022).

Mutational pleiotropy

Although novel mutations are thus random with respect to an organism’s current needs and beneficial mutations do not arise in higher frequency in response to changing environmental conditions (Lenski and Mittler 1993; Svensson and Berger 2019), we might still ask more fine-grained questions about the phenotypic effects of novel mutations. One such question is the distribution of fitness effects, abbreviated DFE (Orr 2005; Wortel et al. 2021). The traditional view is that the vast majority of novel mutations are deleterious, or slightly deleterious (Orr 2005; Wortel et al. 2021). Although novel mutations are random with respect to fitness, a random change in phenotypic space will necessarily move a population that is near its fitness optimum away from that optimum rather than closer to
it (Fisher 1930; Svensson and Berger 2019). This basic feature of the mutational process makes claims from some critics of the current evolutionary framework that mutations are somehow “purposeful” and directed towards organismal needs rather bizarre, as seen in e. g. the writings of Dennis Noble (Noble 2013, 2015, 2017, 2021).

One important question is the extent, consequences and evolutionary origin of mutational pleiotropy, i. e., that novel mutations are typically not isotropic in their expression but show correlated phenotypic effects (Svensson and Berger 2019; Svensson 2022). In other words, novel mutations affecting one trait also tend to affect other traits (Figs. 2, 3, 4), something which evolutionary biologists call mutational pleiotropy (Jones et al. 2014; Svensson et al. 2021; Svensson 2022). Conversely, lack of mutational pleiotropy is termed isotropism and describes a hypothetical situation when two traits are entirely uncorrelated with each other (Gould 2002; Pigliucci 2019). Isotropism seems unlikely, however, given that additive genetic variances and covariances are seldom zero. Massimo Pigliucci has argued that isotropy was the default assumption in the MS in much of contemporary evolutionary biology (Pigliucci 2019), something which is strongly disputed by others (Svensson and Berger 2019; Svensson 2022). The claim that isotropy has been the default

![Fig. 2](image-url) Some possible relationships between the genetic variance–covariance matrix \((G; \text{in grey})\) and the mutational variance–covariance matrix \((M; \text{in black})\). For simplicity, I illustrate the relationships between two traits (“Trait 1” and “Trait 2”, respectively), and the relative size of the circles and ellipses are not intended to accurately reflect the relative magnitudes (i. e., \(M\) is much smaller in magnitude than \(G\), but has been enlarged in size for illustrative purpose). A. The two traits could be entirely uncorrelated with each other in both \(G\) and in \(M\), as illustrated by circles without any eccentricity or orientation. This is the so-called “isotropy assumption”, which has been claimed by some biologists to be the default expectation in evolutionary biology and by the architects of the MS (Gould 2002; Pigliucci 2019). Alternatively, the two traits could be correlated with each other (B-D), either in \(G\) (B) or in both \(G\) and \(M\) (C-D). When the traits are correlated with each other in both \(G\) and \(M\), mutational pleiotropy and the pleiotropy of standing genetic variation could either be aligned (C) or mis-aligned (D). Evolutionary biologists are increasingly appreciating that scenarios C-D are common, contrary to the isotropy assumption in A, claimed to be the default expectation by some biologists (Gould 2002; Pigliucci 2019). Recent quantitative genetics research on fruit flies \(Drosophila melanogaster\) (E) have revealed that \(G\) and \(M\) and the between-species divergence matrix \((R)\) tend to be aligned with each other for wing morphological traits (F)(Houle et al. 2017), raising questions about the evolutionary origin and consequences of mutational pleiotropy
Fig. 3 How correlational selection can build up, strengthen or break down genetic correlations between traits depending on the shape and orientation of the selective surface (\(\omega\)), illustrated as a series of contour plots surrounding an adaptive fitness peak. An element of \(\mathbf{G}\) in the form of a bivariate correlation between two traits ("Trait 1" and "Trait 2", respectively) is shown in grey ellipses or spheres. It is shown how this genetic correlation changes during the ontogeny, due to the action of correlational selection (from left to right). A. When a genetic correlation is absent or very weak, but there is a fitness ridge in the adaptive landscape, correlational selection can build up and promote a genetic correlation that becomes aligned with the selective surface (Cheverud 1984; Phillips and Arnold 1989; Sinervo and Svensson 2002; Svensson et al. 2021). B. In contrast, when there is a genetic correlation that is mis-aligned with the fitness ridge, correlational selection can reduce the correlation in magnitude so that it becomes aligned with the selective surface.

Fig. 4 Schematic and principal relationship between \(\mathbf{M}\) and \(\mathbf{G}\) during the life-cycle and across generations. Two bivariate correlations (here termed “1” and “2” for simplicity), estimated during different parts of the life-cycle are shown. Briefly, every generation there is an influx of novel mutations (captured by \(\mathbf{M}\)) to \(\mathbf{G}\), the latter which is also shaped multivariate selection, genetic drift and sampling error. After selection, \(\mathbf{G}\) is transmitted to the next generation. Novel mutations enter the population, and the cycle starts over again. In this simplified example, one of the bivariate correlation (2) changes, whereas the other one (1) remain unaffected. The degree of similarity between \(\mathbf{M}\) and \(\mathbf{G}\) will depend, among other factors, on the strength of correlational selection that shapes the genetic correlations in every generation and the transmissibility of these effects across generations. The degree of similarity between \(\mathbf{G}\) and \(\mathbf{M}\) is ultimately an empirical question that will be specific to each study system, although it is likely there will always be some structural similarity.
assumption in evolutionary biology is contradicted by extensive theoretical and empirical work on mutational pleiotropy in evolutionary quantitative genetics (Lande 1980; Steppan et al. 2002; Svensson and Berger 2019). Thus, mutational pleiotropy rather than isotropy, as claimed by Pigliucci (Pigliucci 2019) is—and should be—the default assumption of the phenotypic effects of novel mutations. But how does such mutational pleiotropy arise evolutionarily, genetically and developmentally and what are the consequences? I discuss these questions in the next section, after first clarifying some basic terms and definitions.

**Triple alignment between M, G and the selective surface**

In quantitative genetics, a well known statistical concept is the matrix containing information about the variances and covariances of phenotypic traits. This matrix is called $G$, which stands for the genetic variance covariance matrix (Lynch and Walsh 1998; Steppan et al. 2002; Dugand et al. 2021) (Fig. 2). Whereas $G$ describes standing genetic variation and covariation of phenotypic traits, another matrix, termed $M$, describes mutational genetic variation and covariation, the so-called mutational variance–covariance matrix (Jones et al. 2003, 2007, 2014; Dugand et al. 2021) (Fig. 2). Finally, we also need to define $\omega$, which is a Gaussian individual selection surface and the matrix describing multivariate selection (Jones et al. 2014; Svensson and Berger 2019; Svensson et al. 2021) (Fig. 3). An alternative term for $\omega$ is $\gamma$, which is the matrix describing multivariate non-linear selection, where the diagonal elements capture disruptive and stabilizing selection on trait variances and the off-diagonal elements describe correlational selection on trait covariances (Svensson et al. 2021; Dugand et al. 2021). Here, I use the term $\omega$, following the terminology in Jones et al. (2014), for consistency.

What is the expected relationship between $M$ and $G$? Is there any meaningful null model against which we can compare these two matrices? Since mutations is the ultimate source of novel genetic input to any population, one would – all else being equal and assuming that selection is not operating – expect close similarity between $M$ and $G$. However, if one takes a life-cycle perspective (Fig. 4) $M$ and $G$ can potentially become quite different from each other. This will be the case if multivariate and correlational selection operates on trait combinations and shape genetic correlations, for which there is abundant empirical evidence, (Sinervo and Svensson 2002; Svensson et al. 2021; Dugand et al. 2021). If one would estimate $G$ during different parts of the life-cycle in natural populations (which is a challenge, given the need for large sample sizes), one would probably find that genetic covariances during the early part and juvenile of the life-cycle would differ quite substantially from genetic covariances during the later part of the life-cycle, i. e., when estimated from sexually reproducing adults (Figs. 3, 4, 5). The reason for this is that $G$ estimated during the early part of the life-cycle–prior to selection–will be more closely aligned with $M$–whereas $G$ estimated during the later part of the life-cycle will also reflect the effects of multivariate selection, that can either strengthen genetic covariances (Fig. 3A) or weaken them (Fig. 3B), depending on the shape of the selective surface ($\omega$). In other words, multivariate selection (called correlational selection when it operates on genetic covariances between different traits) can either strengthen or weaken these genetic covariances during the life-cycle and make $G$ and $M$ more different from each other than would be expected in the absence of selection (Fig. 3).

However, absence of any correlation between $G$ and $M$, would imply that $G$ would not be a meaningful measure of long-term evolutionary constraint (Reddiex and Chenoweth...
In practice, $G$ and $M$ are likely to show some structural similarity to each other, although the discrepancy between them will reflect the joint actions of mutations, drift and multivariate selection (Jones et al. 2003, 2007; Arnold et al. 2008; Dugand et al. 2021). If $G$ is mainly shaped by mutation and drift, we would expect it to be proportional to $M$, whereas if $G$ is instead mainly shaped by the multivariate selection surface ($\omega$) it will to a greater extent reflect the underlying adaptive landscape (Cheverud 1984; Arnold et al. 2008; Svensson et al. 2021). We should therefore not be too surprised that there will be some structural similarity between $M$ (novel mutational input) and $G$ (standing genetic variation) and that these two matrices will be aligned to some extent, although they will of course not be identical (Fig. 4) increasing empirical evidence has also revealed that correlational selection can build up, strengthen or weaken genetic covariances between phenotypic traits both during the course of the life-cycle and across generations (Sinervo and Svensson 2002; Svensson et al. 2021). In reptiles, insects, fish and birds there is evidence that correlational selection has strengthened genetic covariances between colour and other signaling traits, behaviour, physiology such as immune defense, personality traits and predator avoidance behaviours (Brodie III 1989, 1992, 2021; Svensson et al. 2001, 2009; Sinervo and Svensson 2002).

Conversely, mutation-accumulation experiments (MA) in the laboratory using the nematode Caenorhabditis elegans and the Australian fruit fly Drosophila serrata indicate that mutational covariances between behaviours, life-history and other phenotypic traits and gene expression traits might often be strong and differ from the corresponding genetic covariances captured by $G$ (Estes et al. 2005; McGuigan et al. 2014b, a; Hine et al. 2018; Dugand et al. 2021). One caveat here is that measurement error might make $M$ and $G$ appear more different than they really are. Nevertheless, given this caveat, these results imply that multivariate selection operates to reduce these strong mutational covariances.

**Fig. 5** Graphical illustration of how mutational pleiotropy for fitness leads to sexual antagonism (intralocus sexual conflict) and a changing intersexual genetic correlation ($r_{m,f}$) during an organism’s ontogeny. Each line represents a single genotype (e.g. family means) and its fitness in males and females. Lines with zero or near-zero slopes are genotypes introduced by novel mutations with similar fitness effects in both sexes (i.e., pleiotropy for fitness across the sexes). Most novel mutations will lower fitness equally in both sexes, i.e., they will be unconditionally deleterious. **Left:** early in ontogeny, novel mutational input every generation leads to a positive intersexual genetic correlation ($r_{m,f}>0$) in early life-stages. Thus, mutation-selection balance builds up a positive intersexual genetic correlation for fitness every generation (Bedhomme and Chippindale 2007). **Right:** after selection has operated during the ontogeny of the organism, low-fitness genotypes have been purged and only those with high fitness--averaged across both sexes–remain in the population. These genotypes tend to be those with sexually antagonistic fitness effects, i.e., those with positive effects on fitness in one sex and negative effects on the other sex. These sexually antagonistic alleles tend remain longer in the population than alleles with sexually concordant effects, contributing to standing genetic variation in fitness and maintaining a negative intersexual genetic correlation for fitness ($r_{m,f}<0$) at mutation-selection balance.
between traits during the course of the life-cycle, i.e., strong mutational pleiotropy is maladaptive and counteracted by correlational selection (Svensson et al. 2021; Dugand et al. 2021). This also suggests that mutational bias introduces maladaptive genetic covariances every generation in a tension against multivariate selection that operates to break down these covariances later in the life-cycle (Dugand et al. 2021; Reddiex and Chenoweth 2021). Comparisons between M and G can therefore reveal how multivariate selection changes the covariance structure generated by mutational input every generation, increasing the discrepancy between mutational and standing genetic variation and covariation (Dugand et al. 2021). Finally, artificial selection experiments on plants have also shown that genetic correlations can be broken or diminished by correlational selection in some cases (Delph et al. 2011) although notably not in others (Conner 2002), the latter presumably reflecting situations when trait covariances are caused by strong pleiotropy that is not easily broken by selection.

These empirical examples suggest a primarily negative role for mutational bias in introducing strong and maladaptive genetic covariances that are later weakened or eliminated by multivariate selection each generation (Dugand et al. 2021; Reddiex and Chenoweth 2021). The realized genetic covariances, as captured by G, will then reflect mutation-selection balance at equilibrium (Fig. 4). This negative view of mutation bias as primarily an evolutionary constraint acting in opposition to selection differs from the more creative and positive role for it that some researchers claim vindicates Mendelian-mutationism and leads to extensive mutation-biased adaptation at the molecular level (Yampolsky and Stoltzfus 2001; Stoltzfus 2006; Stoltzfus and Yampolsky 2009; Stoltzfus and Cable 2014; Stoltzfus and McCandlish 2017; Gomez et al. 2020). Mutation bias can thus potentially be important also as an evolutionary constraint although this does not render it such a creative role in adaptive evolution that some of its proponents want to promote it to.

The increasing awareness of multivariate and correlational selection have stimulated models of how G, M and $\omega$ could jointly evolve and become aligned with each other (Jones et al. 2014; Svensson and Berger 2019; Svensson et al. 2021). Specifically, the evolution of epistatic relationships can result in “triple alignment” between G, M and $\omega$ (Jones et al. 2014). In these models, not only does G evolve to reflect the underlying selective surface as was suggested long time ago (Cheverud 1984), but so does M (Jones et al. 2014) (Fig. 2C). Superficially, this might give the false impression that novel mutations are “adaptive” or “directed” towards high fitness, as implicitly or explicitly claimed by some proponents of directed mutations (Shapiro 2011; Noble 2013, 2015, 2017, 2021) but this would an erroneous conclusion (Svensson and Berger 2019). Instead, such alignment between G and M should be interpreted as novel mutations at loci that have been shaped by past multivariate selection “inherit” adaptive pleiotropy and epistatic relationships from the ancestral alleles from which they originate (Svensson and Berger 2019). Hence, adaptive evolution of pleiotropy by multivariate selection does not only directly shape standing genetic variances and covariances of G, but does also indirectly shape mutational variances and covariances of M, even though these novel mutations have not been directly exposed to selection (Jones et al. 2014; Svensson and Berger 2019; Svensson et al. 2021). M can also reflect the effects of past selection for mutational robustness (Wagner 2005; Svensson and Berger 2019) and that selection could have lowered mutation rates in key genes where mutations could have severe and negative fitness effects (Monroe et al. 2022). In brief: novel mutations inherit the phenotypic expression profiles of the ancestral alleles at those loci where these novel mutations originated from, resulting in a long-term evolutionary “memory” of past correlational selection that shapes both mutational and genetic variances and co-variances (Svensson et al. 2021). Some biologists also argue that basic principles of development,
modularity and robustness makes structural similarity between $M$ and $G$ almost inevitable (Hernández et al. 2022).

Direct empirical support for all the links in the causal chain discussed above is still limiting, although Houle and colleagues have shown that $G$, $M$ and the macroevolutionary divergence matrix ($R$) of wing morphology in Drosophila showed remarkable alignment across species encompassing over 40 million years of evolution (Houle et al. 2017, 2020)(Fig. 2D and E). Hence, $M$ could accurately predict macroevolutionary divergence as captured by $R$, suggestive of mutation-driven neutral evolution of wing morphology with little or no role for selection (Houle et al. 2017). However, the difference among species was far less than would have been expected under a purely neutral model, i. e., if mutation had been operating alone these species would have been much more divergent in wing morphology than they actually were (Houle et al. 2017; Svensson and Berger 2019). This suggests that stabilizing multivariate natural selection maintains a similar wing morphology across species over long macroevolutionary time scales, perhaps by operating on the pleiotropic relationships underlying the variances and covariances of the wing phenotype (Svensson and Berger 2019). Although the selective surface ($\omega$) was not measured in the study by Houle et al. (2017), the results are compatible with and consistent with the model by Jones et al. (2014) and the prediction that $M$, $G$ and $\omega$ should become aligned with each other (Svensson and Berger 2019). Thus, the alignment between $M$ and $G$ is exactly what we would expect from this model, rather than the naïve expectation that $M$ should lack mutational pleiotropy and that mutational variation would be isotropic (cf. Figure 2A and C). Against this background, it is somewhat unexpected that Houle et al. (2017) seemed surprised over the alignment between $M$ and $G$, as this is what would be expected under a model where novel mutations partly inherit the adaptive pleiotropy and epistatic effects of their allelic ancestors (Jones et al. 2014; Svensson and Berger 2019). It is easy to get the impression that Houle et al. (2017) expected $M$ to show isotropy and that they were surprised by the extensive mutational pleiotropy they found, especially as they later rather bluntly dismissed “the vaguer hypothesis that mutation is reshaped to match the historical strength of selection” as being “implausible” in a later follow-up study (Houle et al. 2020), without motivating this further, nor did they refer to Jones et al. (2014). Clearly, these authors do not seem to believe in this explanation for why $M$ and $G$ are aligned, although they offer no alternative explanation to explain their results (Houle et al. 2020).

The mutational process, sex differences, sexual selection and sexual antagonism

So far, the discussion has focused on mutation bias and mutational pleiotropy for a few loci or phenotypic traits. However, often we are more interested in fitness itself, or phenotypic traits closely connected to fitness, such as fitness components and secondary sexual characters. The mutational process and mutation bias has also important roles for these more inclusive phenotypes, which I will briefly discuss here.

First, males are known to have higher germline mutation rates than females, a phenomenon also called “male-driven evolution” (Li et al. 2002). Although there are several explanations for such male mutation bias, the most popular one is that there are many more cell divisions in spermatogenesis than in oogenesis, increasing the per-generation scope for DNA replication errors (Ellegren and Fridolfsson 1997). Second, theories for the evolution of sex, sex differences and sexual selection assume that male’s
demographic contributions to population fitness and population growth is low or negligible compared to that of females (Agrawal 2001; Siller 2001). Consequently, if novel and recessive deleterious mutations mainly reduce male fitness, and low-quality males are rejected by female choice or such males are at disadvantage in male-male competition, intra- or intersexual selection can purge the genome from deleterious mutations, reduce the mutation load and increase mean population fitness (Dolgin et al. 2006; Whitlock and Agrawal 2009; McGuigan et al. 2011). One requirement for this process to operate efficiently is that there is mutational pleiotropy between male mating success and non-sexual fitness components such as female fecundity (McGuigan et al. 2011). If such mutational pleiotropy exists, sexual selection through male mating mating success will also increase female fitness and thereby population mean fitness as a correlated response (McGuigan et al. 2011).

Other situations where mutation supply or mutation bias can play major roles are in models of Fisherian sexual selection (Pomiankowski et al. 1991) and in the so-called “genic capture” model of condition-dependent sexual selection (Rowe and Houle 1996). In the former model, it was shown that if mutations affecting a male secondary sexual trait are biased in their phenotypic effects so that they tend to reduce secondary sexual traits to a greater extent than to increase trait values, costly female preferences could be maintained, increasing the likelihood of Fisherian sexual selection (Pomiankowski et al. 1991). This is a model of how biased phenotypic effects of mutations affect sexual selection and maintain costly female choice. Similarly, condition-dependent secondary sexual characters typically have quite high additive genetic variance (Rowe and Houle 1996). Male variation in condition can then reflect genome-wide variation in mutational input if most loci in the genome contribute to generate genetic variation in condition (Rowe and Houle 1996). Even though per-locus mutational input to condition would be low, overall mutation supply across the genome would be large. Since condition is a large mutational target, mutations would tend to reduce male condition, re-generating additive genetic variance every generation in a balance against sexual selection (Rowe and Houle 1996).

Finally, if there is mutational pleiotropy between male and female fitness, this can have strong implications for our ability to detect sexual antagonism from intralocus sexual conflict (Rice and Chippindale 2001; Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009) (Fig. 5). Due to different male and female fitness optima and positive intersexual genetic correlations between male and female phenotypes (Poissant et al. 2008), intralocus sexual conflict will arise when alleles that increase the fitness of one sex decrease the fitness of the other sex (Chippindale et al. 2001; Foerster et al. 2007; Svensson et al. 2009). The expected outcome of such intralocus sexual conflict is a negative genetic correlation for adult (reproductive) fitness (Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009) (Fig. 5). However, negative intersexual genetic correlation for fitness are not always found, because mutation-selection balance introduces new deleterious mutations every generation and tend to build up positive genetic covariance for fitness between the sexes when we expect it to be negative (Bedhomme and Chippindale 2007) (Fig. 5). In some cases, intersexual genetic covariance for fitness could be positive early in ontogeny, due to mutational pleiotropy, but it switch to become negative during the adult (reproductive) stage (Fig. 5) (Chippindale et al. 2001). Although such a switch in the sign of the intersexual genetic covariance have not been found in all studies and there are exceptions (Svensson et al. 2009), this underscores the importance of considering mutational fitness effects across the entire life-cycle and not only during the adult life-stage (cf. Fig. 3, 5).
Conclusion

Here I have discussed the fitness effects of mutations, the random nature of the mutational process and what it means and the role of mutational pleiotropy in evolution. Mutations play a crucial role in the evolutionary process, albeit they are neither “directed” nor do they show signs of “purpose” as claimed by some critics of evolutionary biology (Shapiro 2011; Noble 2013, 2015, 2017, 2021). Neither is adaptive evolution “mutation-driven” as claimed by others (Nei 2013). Such claims about the role of mutations in the evolutionary process paint a misleading picture of the state of contemporary evolutionary theory. However, recent empirical research on mutational pleiotropy have shown a surprisingly strong alignment between M and G (Houle et al. 2017) but multivariate selection theory can explain how such alignment can evolve through shared underlying epistatic relationships that shape mutational and standing genetic variation (Jones et al. 2014; Svensson et al. 2021). In addition, selection for mutational robustness and lowered mutation rates in key genes with strong effects of fitness can also potentially shape both M and G (Wagner 2005; Svensson and Berger 2019; Monroe et al. 2022). Laboratory experiments have demonstrated how multivariate selection can shape pleiotropy during the course of the life cycle (Estes et al. 2005; McGuigan et al. 2014b, a; Hine et al. 2018; Dugand et al. 2021; Reddiex and Chenoweth 2021) and our understanding of the evolutionary feedbacks, causal and mechanistic links between M and G (Fig. 4) is gradually increasing (Svensson and Berger 2019; Svensson et al. 2021).

My overview over the fitness effects of mutations gives no support to claims that mutation bias and mutation-biased adaptation make it necessary to reconsider and incorporate Mendelian-mutationism and other forms of internalism in to evolutionary theory, as argued by some biologists (Stoltzfus 2006; Stoltzfus and Yampolsky 2009; Stoltzfus and Cable 2014). Mutation bias can and does give rise to directionality at the molecular level in neutral evolution (Sueoka 1988; Weng et al. 2019; Monroe et al. 2022) and it certainly has potential to influence the underlying genetic architectures of phenotypic traits also in adaptive evolution (Fig. 1), but it must be aided by genetic drift or selection to result in mutation-biased adaptation (Lynch 2007; Svensson and Berger 2019). Mutation bias and mutation-biased adaptation are incorporated in the contemporary evolutionary framework as stochasticity and historical contingencies underlying the genetics of adaptation. A possible exception where internalism and directed mutations could could play some role are transposable elements (TE:s) in genomic evolution that can cause long-term trends and even affect phenotypic performance (Gregory et al. 2016). This phenomenon is perhaps better merged with multi-level selection theory, where the result is a balance between higher- and lower-level selection, at the organismal and molecular levels, respectively (Gregory et al. 2016).

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