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Tansley insight

What does the distribution of fitness effects of new mutations reflect? Insights from plants

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Summary

The distribution of fitness effects (DFE) of new mutations plays a central role in molecular evolution. It is therefore crucial to be able to estimate it accurately from genomic data and to understand the factors that shape it. After a rapid overview of available methods to characterize the fitness effects of mutations, we review what is known on the factors affecting them in plants. Available data indicate that life history traits (e.g. mating system and longevity) have a major effect on the DFE. By contrast, the impact of demography within species appears to be more limited. These results remain to be confirmed, and methods to estimate the joint evolution of demography, life history traits, and the DFE need to be developed.

I. Introduction

Without mutations there is no evolution. The path evolution will take depends, to a large extent, on how many mutations enter the population each generation and how they affect fitness. This general picture was, by and large, firmly established by the work of Fisher, Wright, and Haldane, and its main tenets have not changed much since then (Charlesworth *et al.*, 2017). However, until recently it was difficult to assess the relative parts played by evolutionary forces at each of these steps since data were not available. This has drastically changed today with the availability of genomic data in many species. Though mutation rates and effects remain intrinsically very difficult to quantify, it is nonetheless possible today to obtain both indirect (i.e. phylogeny-based) and direct (i.e. pedigree-based) genome-wide estimates of

mutation rates – see Moorjani *et al.* (2016) and Chintalapati & Moorjani (2020) and references therein – as well as to characterize the distribution of fitness of mutations. We will focus on the latter in this article.

Mutations can be classified according to their fitness effects: deleterious, neutral, and beneficial. All agree that most mutations are most often either deleterious or neutral and that the contribution of highly deleterious and beneficial mutations to standing variation is limited (Eyre-Walker & Keightley, 2007). The highly deleterious mutations are quickly eliminated from the population and the beneficial mutations are likely rare. However, agreement ends here, and there are contrasted views on the relative size and role in evolution of the different fitness classes (Jensen *et al.*, 2018; Kern & Hahn, 2018). In part, these disagreements reflect different views on evolution and on the relative importance of the forces driving it.

But, in no lesser part, these disagreements simply stem from the inherent difficulty to characterize the fitness effects of mutations.

Different methods have been devised to characterize the fitness effect of mutations from sequence data. A first group of methods assumes that mutations occurring at nucleotide sites that are highly conserved across species are likely to be deleterious (Ng & Henikoff, 2003; Davydov *et al.*, 2010). Accordingly, these methods assign a score to a site that measures how much the site departs from the variation that would be observed in a multispecies alignment if the sites were evolving neutrally. The resulting score is effectively measuring how deleterious the mutations are at a given site. The pros of this approach are that it makes single-sites predictions, is readily available for an increasing number of species, can incorporate covariates from functional genomic studies, and does not depend on elusive population genetics parameters (e.g. effective population size). However, it can be misleading for predictions on the fitness effect of genetic variation currently segregating as it does not directly estimate fitness effects and focuses exclusively on deleterious mutations. This approach was recently used to characterize the impact on fitness of amino acid changing mutations in a host of plant species; for example, poplars (*Populus ilicifolia*; Z. Chen *et al.* 2020) and sorghum (*Sorghum bicolor*; Valluru *et al.*, 2019).

In contrast to methods using scores based on conservation/divergence across species, methods in the second group leverage polymorphism within species and estimate an underlying distribution of fitness effects (DFE) of new mutations. This is achieved by modelling the site frequency spectrum (SFS) at putatively neutral and selected sites, for instance, synonymous and nonsynonymous sites. The DFE of new mutations is the distribution of the relative frequencies of selection coefficients s , extending from strongly and weakly deleterious, through neutral mutations, to slightly and strongly advantageous (Moutinho *et al.*, 2020). The most recent estimation methods consider both deleterious and beneficial mutations, although we stress that estimating the fraction of beneficial mutations is intrinsically challenging simply because beneficial mutations are rare and have a modest impact on the SFS. In contrast to methods relying exclusively on conservation scores, methods based on the DFE estimate the effect of mutations currently segregating and do not assume conservation of effects across species. Estimates of the DFE from SFS data have been reported across many animal and plant species (Galtier, 2016; Chen *et al.*, 2017; Castellano *et al.*, 2019).

Being able to estimate the DFE is a prerequisite, and this remains a difficult statistical problem. Understanding what factors determine the DFE would greatly help focusing our efforts on the most important sources of variation (Fig. 1). It should be noted here that though being able to estimate a DFE reliably is crucial to assessing competing models of molecular evolution, obtaining a reliable estimate of the DFE is also important to characterize the evolution of species: mutations rates and the DFE are not fixed entities but instead are under the same evolutionary forces as any other complex phenotypic trait. As they evolve, so will other key biological features of organisms; for instance, life history traits, mating systems, ploidy level or genome structure, and population history (demography, environment). In turn, changes of these features will influence the evolution of the DFE.

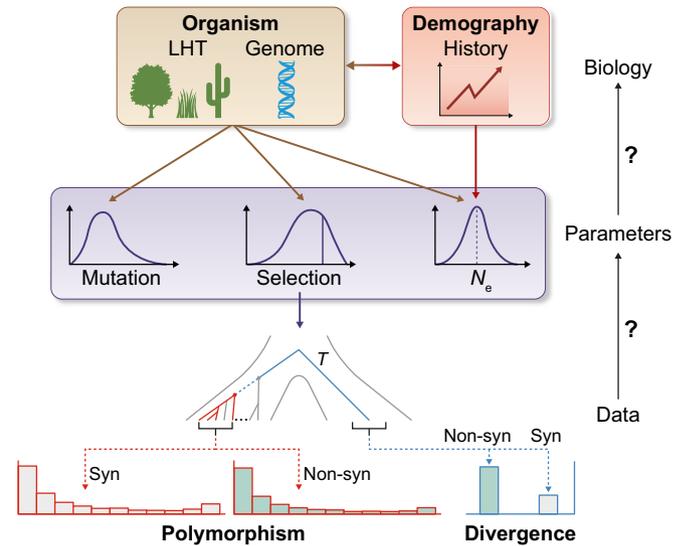


Fig. 1 Inverting the map: exploiting genome-wide patterns of polymorphism and divergence to learn about mutation and their fitness effects. The left side of the figure sketches a causal path from proximal evolutionary causes at the top to the patterns in the data used to estimate the distribution of fitness effects (DFE) of new mutations at the bottom. The right side pictures the inference path, from data to the biological factors that have shaped the DFE. T is the divergence time between the focal species and the outgroup species. LHT, life-history traits; N_e , effective population size; Non-syn, nonsynonymous; Syn, synonymous.

II. DFE and related quantities

The estimation of the fitness effect of new mutations is based on a fundamental intuition: the fitness effect of a new mutation influences the frequency at which it segregates in a population. However, demography also affects allelic frequencies, making it crucial to tease apart the effect of demography and selection. In brief, this is done by comparing the SFS of putatively neutral mutations (typically synonymous ones) only affected by demography to mutations under selection (typically non-synonymous ones) affected by both demography and selection, as further described in Box 1. Importantly, as usual in population genetics, these methods provide estimation of the population-scale selection coefficient $N_e s$, the product of effective population size N_e and selection coefficient s , not directly s alone. It means that in small populations, a higher proportion of mutations is mostly affected by drift and behaves like neutral ones, which is the central idea of the nearly neutral theory of molecular evolution (Ohta, 1973).

Many studies choose to focus on quantities related to the DFE, which may be simpler to calculate. Two important statistics are the ratio of nucleotide diversity at nonsynonymous and synonymous sites π_N/π_S and the proportion of adaptive nonsynonymous substitutions α (Smith & Eyre-Walker, 2002; Galtier, 2016). The ratio π_N/π_S roughly measures the proportion of effectively neutral mutations; that is, mutations for which $|N_e s| \lesssim 1$ (Ohta, 1973). It gives a global measure of the efficacy of selection relative to drift. The proportion of adaptive nonsynonymous substitutions α has attracted a lot of attention. Initially, α was inferred using an

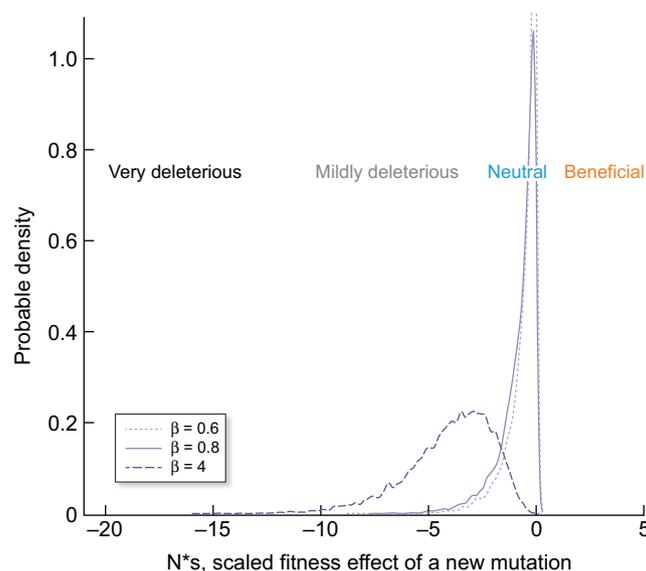
extension of the McDonald–Kreitman test, a test of neutrality that compares the number of polymorphisms with the number of substitutions in two types of sites, synonymous and nonsynonymous. α can then be defined as $1 - (D_s P_n)/(D_n P_s)$ (D , divergence; P , polymorphism; s , synonymous; n , nonsynonymous). A related quantity is the rate of adaptive nonsynonymous substitutions relative to the mutation rate, ω_a (Galtier, 2016). However, these estimates were shown to be biased – in particular by the presence of slightly deleterious mutations – and have since then been replaced by estimates derived from the DFE and accounting for demography (Keightley & Eyre-Walker, 2007; Galtier, 2016; Tataru *et al.*, 2017; Tataru & Bataillon, 2019; and see Box 1).

III. The DFE and the biology of plants

Plants harbor a large diversity of life-history traits, genome features, and demographic histories, and their impact on the DFE has just started to be investigated. First, because the DFE depends on N_e , we certainly expect demography to matter. However, it is important to distinguish contingent demographic processes – for instance, changes related to glacial cycles – from those that are related to the intrinsic properties of the species. Historical demographic events will seriously affect the estimation of the DFE and their interpretation, but they can, in principle at least, be accommodated (Brandvain & Wright, 2016) and will not have permanent effects.

Box 1 Estimation of the distribution of fitness effects.

Most estimation methods model information from the site frequency spectrum (SFS) for two classes of nucleotide changes: putatively neutral ones, generally synonymous or four-fold degenerate ones, and putatively selected ones, classically nonsynonymous or four-fold degenerate changes (Bataillon & Bailey, 2014; Moutinho *et al.*, 2020). The SFS describes polymorphism in a sample of chromosomes by counting the number of segregating sites at which a mutation is represented by one copy, two copies, and so on. If we can infer the ancestral/derived allele at a polymorphic site, we will obtain an unfolded SFS with $n - 1$ classes for a sample of size n . If we do not know the ancestral site, the SFS will be folded with $n/2$ or $(n + 1)/2$ classes depending on whether n is even or odd. Unfolded SFSs are more informative, but identifying the ancestral state is still fraught with difficulties and misidentification can bias distribution of fitness effects (DFE) estimates (Keightley & Jackson, 2018). The nonsynonymous SFS will be affected by selection. For instance, in the presence of slightly deleterious mutations, one expects an excess of rare variants compared with the neutral SFS in a population at mutation drift equilibrium. Unfortunately, selection is not the only evolutionary force affecting the SFS. Demography, too, will influence it, and, for example, a similar excess of rare variants will result from population expansion or a not too recent bottleneck. One main challenge, therefore, is to distinguish between the effects of selection and demography. This is achieved by assuming that synonymous sites are evolving under neutrality and can be used to infer demography and correct for it when estimating the effect of selection from the nonsynonymous SFS. This assumption is central to all methods inferring the DFE from the SFS. Different maximum likelihood methods exist to estimate the DFE. Usually, they assume that the effects of deleterious mutations are gamma distributed, with a mean $N_e s$ (N_e , effective population size; s , selection coefficient) and a shape parameter β (see Box Fig. 1). Otherwise, they primarily differ in the way they correct for the effects of demography and whether they require divergence data and consider beneficial mutations (Eyre-Walker *et al.*, 2006; Keightley & Eyre-Walker, 2007; Galtier, 2016; Tataru *et al.*, 2017; Tataru & Bataillon, 2019). Moutinho *et al.* (2020) reviewed the different methods. Generally, the DFE is estimated at the species or population level, but recent implementations also allow testing for invariance or change of the DFE across species or gene categories (Tataru & Bataillon, 2019) or correlation of DFEs across populations of the same species (Huang *et al.*, 2021).



Box Fig. 1 Three hypothetical, gamma distributed negative DFE. The overall shape of the DFE is governed by the parameter β .

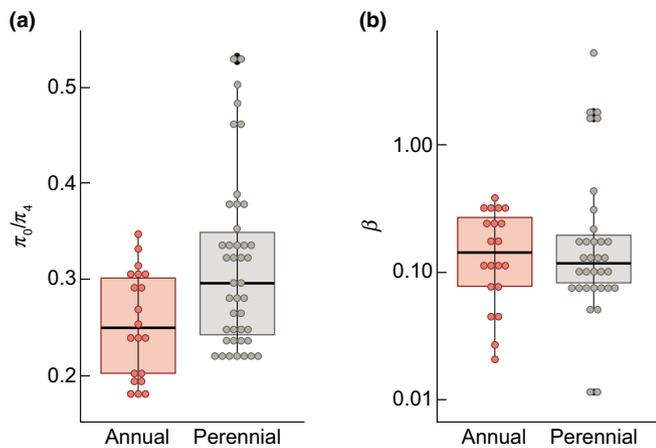


Fig. 2 Box plots of (a) the π_0/π_4 ratio and (b) the shape parameter β of the negative part of the distribution of fitness effects (DFE) for annual and perennial plant species. Data are from J. Chen *et al.* (2017, 2020, 2021). π_0/π_4 is the ratio of nucleotide diversity at zero-fold and four-fold degenerate sites and is used as a proxy for π_N/π_S . When estimating the shape of the negative part of the DFE, β , one assumes that the negative DFE follows a gamma distribution with shape parameter β . The horizontal line gives the median, circles are individual values, and the box gives the interquartile range.

Life-history traits can also affect the effective size of a species, and thereby the proportion of nearly neutral mutations. For example, N_e is predicted to be much lower in selfing than in outcrossing species (Charlesworth, 2003). A second idea is that life-history traits can affect the strength of selection experienced by a species and the speed of adaptation to changing environment. For example, long-lived species likely experience stronger and more variable selective pressure and may adapt more slowly (Petit & Hampe, 2006).

So far, most studies have not made explicit comparisons of the DFE but instead have focused on specific aspects of the DFE in relation to a given hypothesis. In a comprehensive study aimed at testing the prediction of the nearly neutral theory of molecular evolution, using 34 animal and 28 plant species, Chen *et al.* (2017) investigated the effect of different life-history traits on the π_N/π_S ratio. As already discussed herein, we expect the π_N/π_S ratio to reflect the proportion of effectively neutral mutations, and so to be inversely related to the effective population size of a species. The π_N/π_S ratio should, therefore, be higher in self-fertilizing species than in outcrossing ones. Indeed, this is what is observed, with the other factor having a major effect being longevity. In fact, although the proportion of effectively neutral mutations was much smaller in outcrossing annuals than in self-fertilizing ones, the proportion of effectively neutral mutations was similar to that in self-fertilizing annuals, indicating a strong effect of longevity. An effect of the reproductive system was also observed by Muyle *et al.* (2020), who tested the effect of dioecy vs gynodioecy vs hermaphroditism on the DFE and on derived statistics in the genus *Silene*. As for selfing vs outcrossing, the change in sexual system is associated with a change in the DFE: dioecious species harbored more diversity, more efficient purifying selection (low π_N/π_S ratio), and evolved with a higher rate of adaptive nonsynonymous substitutions ω_a . The impact of life-history traits on other properties of the DFE, such as

its shape parameter for the negative part (Box 1), was less clear, but a further study (J. Chen *et al.*, 2020) found a clear difference between selfers and outcrossers (see also Douglas *et al.*, 2015). Based on some of the species used in J. Chen *et al.* (2017, 2020) and a few additional ones, we recently estimated the full DFE in annuals and perennial species. A comparison of two DFE parameters between these two groups is given in Fig. 2(a,b). As already observed, there is a clear difference in the π_N/π_S ratio; but the DFE shape is similar, with perennials tending to have a wider range of shapes (Fig. 2b).

In contrast to the profound effect of life-history traits on the DFE and derived summary statistics such as π_N/π_S , α , or ω_a , the effect of demography within species or domestication seems more limited. Particularly striking is the limited effect of domestication on π_N/π_S (J. Chen *et al.*, 2017, 2020). As shown in Fig. 3(a), domestication led to a very severe decrease in synonymous nucleotide diversity π_S , but this was not accompanied by a similar change in π_N/π_S , which, on the contrary, appears extremely stable. Similarly, variation in levels of neutral nucleotide diversity across populations in a range of different species was not associated with commensurate changes in π_N/π_S (Fig. 3b). Lack of marked differences between populations within the same species does not preclude differences between species that have experienced very different demographic histories. For example, Jaramillo-Correa *et al.* (2020) compared two parapatric Mediterranean pine species, stone pine (*Pinus pinea*) and maritime pine (*Pinus pinaster*). The former went through a severe bottleneck and has today an extremely limited genetic variation compared with maritime pine ($\pi_S = 0.00043$ vs $\pi_S = 0.0045$, with corresponding $\pi_N/\pi_S = 0.45$ vs $\pi_N/\pi_S = 0.26$). The DFEs inferred in each species were similar, but stone pine had a significantly higher proportion of slightly deleterious mutations and maritime pine a higher proportion of highly deleterious mutations. However, stone pine can be divided into a western and an eastern cluster, and no differences were observed between the DFEs of these two clusters in spite of marked differences in effective population sizes ($N_e(\text{west}) = 5620$ vs $N_e(\text{east}) = 841$). It therefore seems that the differences observed between the two pine species may not be entirely due to differences in demographic history, at least not the recent one. Another striking illustration of the joint effect of demography and mating system is provided by the comparison of populations of *Arabidopsis alpina* (Laenen *et al.*, 2018). Southern European populations have a nucleotide diversity varying between 0.0046 and 0.0080, whereas Scandinavian ones have a mean nucleotide diversity more than ten-fold smaller (0.0002). Within the southern European populations, π_N/π_S varied between 0.27 and 0.29, whereas the value was 0.39 in Scandinavia. Scandinavian populations, unlike their southern European counterparts, experienced a severe bottleneck during the Last Glacial Maximum. Perhaps more importantly, they exhibit a much higher selfing rate. Considering results obtained in other species, the differences in DFE between the two groups of populations might primarily reflect the change in mating system rather than be a consequence of differences in past demography. A similar conclusion can be drawn when comparing deleterious load between sorghum (a selfer) and maize (*Zea mays*, an outcrosser) (Lozano *et al.*, 2021).

Finally, genome properties will also affect the DFE. For instance, GC-biased gene conversion in both *Arabidopsis thaliana*,

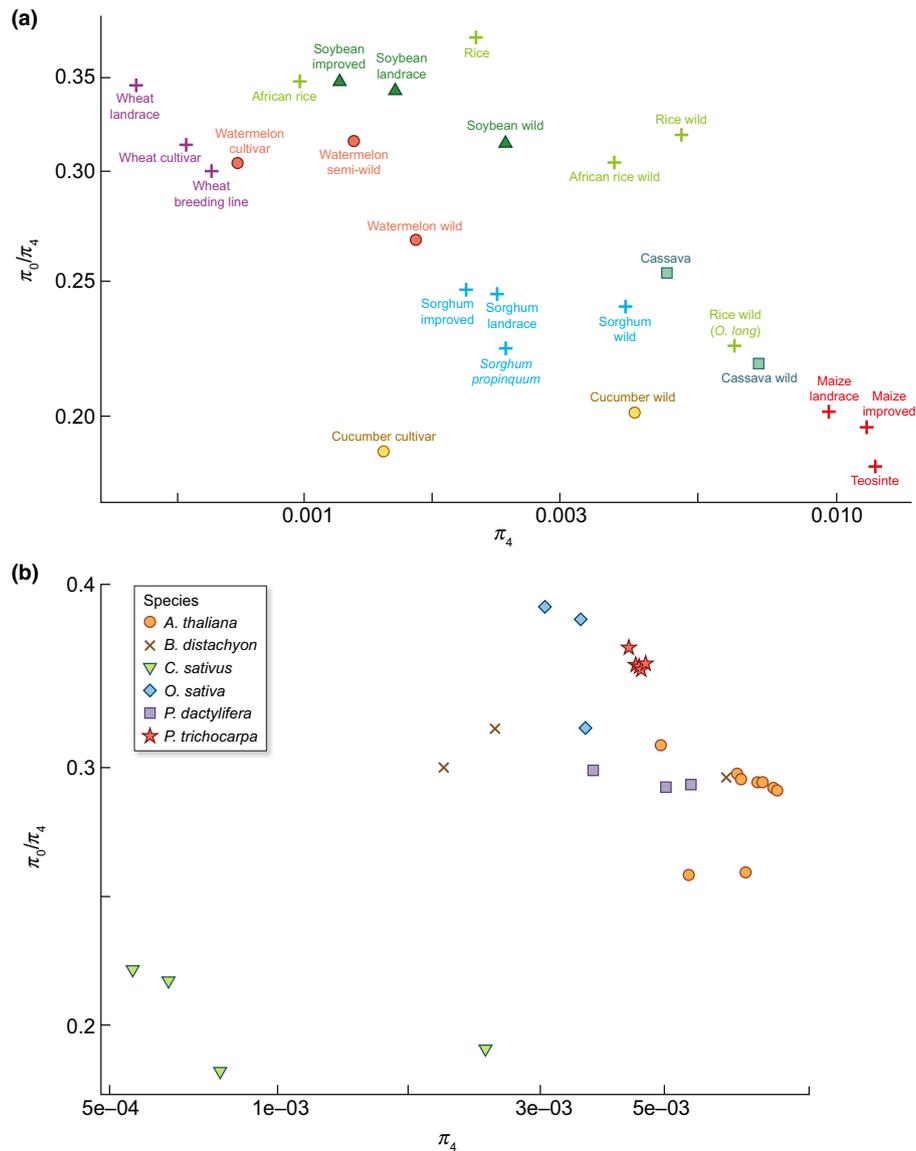


Fig. 3 Difference in the π_0/π_4 ratio (a) between domesticated species and their wild relatives and (b) between populations within species (*Arabidopsis thaliana*, *Brachypodium distachyon*, *Crocus sativus*, *Oryza sativa*, *Phoenix dactylifera*, *Populus trichocarpa*). Data are from Chen *et al.* (2017). π_0/π_4 is the ratio of nucleotide diversity at zero-fold and four-fold degenerate sites and is used as a proxy for π_N/π_S .

Arabidopsis lyrata, and *Capsella grandiflora* contribute to a genome-wide signal of decreased efficacy of selection (Hämälä & Tiffin, 2020). The effect of polyploidy has not been studied extensively yet, but available studies indicate relaxed selection in polyploids (Douglas *et al.*, 2015) and a strong parental legacy effect on the subgenomes (Kryvokhyzha *et al.*, 2019). One could therefore expect the DFE of the subgenomes to differ among themselves and also from the parental species' DFEs.

In general, it appears that the DFE is primarily determined by the biological properties of the species, here captured by traits such as mating system or longevity (and maybe polyploidy), and, secondarily, by their demographic history – but see Willi *et al.* (2020) for a case where demography and mating system apparently have a similar impact. A possible reason is that the DFE is weakly sensitive to short-term demographic variations (Brandvain & Wright, 2016) but influenced more by long-term trends, well captured by basic

biological characteristics of a species, as also proposed for polymorphism patterns in animals (Romiguier *et al.*, 2014). Of course, this is a somewhat arbitrary separation, as a great deal of the demography of a species is also determined by its biology and it is, intrinsically, difficult to separate the effect of selection and demography, even though it would be highly desirable (Li *et al.*, 2012).

IV. Conclusions

The first attempts to estimate the DFE only date back to the early 2000s, and much development in estimation methods and gathering of data has already occurred. Given the rate at which high-quality genomic data sets become available, we expect numerous estimates of the DFE across plant species to be available soon. This should soon allow us to combine phylogenetic and

population genetics approaches within an integrative framework (Brevet & Lartillot, 2021). This will be an important step for a more robust understanding of the factors shaping the DFE and assessing its evolutionary stability. A truly comparative approach should allow us to ascertain some of the trends observed through comparisons of population genetic estimates of the DFE across species. Another promising path is to use knowledge about the genome structure to improve estimation of the DFE. Whereas some methods rely on machine learning and require a large amount of information that is only available in a handful of species (Huang & Siepel, 2019), others should be easily implemented in numerous less well studied species (Chen *et al.*, 2021). Ultimately, this should help to tease apart the effects of life history and genomic traits vs demography (basically N_e) on the DFE. Finally, when possible (i.e. with species with short generation times), these efforts should be supplemented by more direct experimental approaches, such as mutation accumulation experiments (Böndel *et al.*, 2019).

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