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A century of theories of balancing selection

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ABSTRACT

Traits that affect organismal fitness are often highly genetically variable. This genetic variation is vital for populations to adapt to their environments, but it is also surprising given that nature – after all – 'selects' the best genotypes at the expense of those that fall short. Explaining the extensive genetic variation of fitness-related traits is thus a longstanding puzzle in evolutionary biology, with cascading implications for ecology, conservation, and human health. Balancing selection – an umbrella term for scenarios in which natural selection maintains genetic variation – is a century-old explanation to resolve this puzzle that has gained recent momentum from genome-scale methods for detecting it. Yet evaluating whether balancing selection can, in fact, resolve the puzzle is challenging, given the logistical constraints of distinguishing balancing selection from alternative hypotheses and the daunting collection of theoretical models that formally underpin this debate. Here, we track the development of balancing selection theory over the last century and provide an accessible review of this rich collection of models. We first outline the range of biological scenarios that can generate balancing selection. We then examine how fundamental features of genetic systems – non-random mating between individuals, ploidy levels, genetic drift, linkage, and genetic architectures of traits – have been progressively incorporated into the theory. We end by linking these theoretical predictions to ongoing empirical efforts to understand the evolutionary processes that explain genetic variation.

Key words: evolutionary theory, population genetics, balancing selection, heterozygote advantage, trade-offs, negative frequency-dependent selection, fitness variation, mathematical modelling.

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I. INTRODUCTION

Throughout nature – from birds, mammals and flies, to flowering plants (Delph & Kelly, 2014; Charlesworth, 2015; Bonnet *et al.*, 2022) – individuals vary genetically in their ability to survive and reproduce, supplying the raw material for evolutionary adaptation. There are two broad schools of thought to explain this abundant genetic variation for fitness and the traits that influence it (Lewontin, 1974; Charlesworth, 2015). One school proposes that selection continually removes genetic variation, while mutation continually replenishes it (Muller, 1950). Under this view, the resulting equilibrium between recurrent mutation and purifying selection ('mutation–selection balance') accounts for most variation for fitness and its components. The second school proposes that genetic variation is maintained by selection: a concept known as 'balancing selection' (Dobzhansky, 1955). Balancing selection can arise from a variety of scenarios, including selection favouring heterozygotes over homozygotes, selection for rare over common genotypes, and selective trade-offs in which genetic variants favoured in some contexts (e.g. seasons, niches, sexes, life-history stages) are disfavoured in others.

Despite considerable debate during the second half of the 20th century (Lewontin, 1974) and recent renewed interest in balancing selection (Fijarczyk & Babik, 2015; Llaurens, Whibley & Joron, 2017; Bitarello *et al.*, 2023), the contribution of balancing selection to the maintenance of variation for fitness and its components remains unresolved (Charlesworth, 2015). Little more than a decade ago, however, the prevailing view was that balancing selection was probably of minor importance in evolution. Summarising the sentiment, Asthana, Schmidt & Sunyaev (2005, p. 30) wrote that "balancing selection […] has not been a significant force in human evolution", while Hedrick (2007, p. 231) similarly suggested that "a low proportion of loci in the human genome are under long-term balancing selection".

Why did this become the prevailing view? First, few empirical examples of balancing selection were clearly documented at the time. The most prominent ones – beta-globin alleles in humans (Allison, 1954), self-incompatibility alleles in outcrossing plants (Emerson, 1938; Wright, 1939), chromosomal inversion polymorphisms in *Drosophila* (Wright & Dobzhansky, 1946), and the major histocompatibility complex alleles in vertebrates (Charlesworth, 2006) – were decades old and seen as outliers. When early genome scans failed to detect polymorphisms under long-term balancing selection (Asthana *et al.*, 2005; Bubb *et al.*, 2006), the view that balancing selection was exceedingly rare was reinforced. Second, balancing selection hypotheses faced several theoretical objections. In particular, ubiquitous balancing selection on the abundant genetic polymorphisms discovered in natural populations (Lewontin & Hubby, 1966; Kreitman, 1983) seemed unlikely given the exorbitant mortality cost ('genetic load') implied by such a hypothesis (Kimura & Crow, 1964; Lewontin & Hubby, 1966), although ecological counterarguments soon tempered this criticism (King, 1967; Milkman, 1967; Sved, Reed & Bodmer, 1967; Wallace, 1975; Clarke, 1979; Agrawal & Whitlock, 2012). Meanwhile, the intuition that genetic trade-offs often generate balancing selection was undermined by theory demonstrating that trade-offs typically result in loss, rather than maintenance, of genetic polymorphism (Maynard Smith & Hoekstra, 1980; Prout, 2000). Finally, models of quantitative traits selected towards an intermediate optimum (i.e. traits under 'stabilising selection') highlighted restrictive conditions for persistent balancing selection at the genetic loci underlying the trait (Wright, 1935; Turelli & Barton, 2004; Johnson & Barton, 2005). The notion that traits are often quantitative and selection is often stabilising (Kingsolver *et al.*, 2001; Sanjak *et al.*, 2018) seemed, therefore, to minimise the role of balancing selection.

Recent advances cast doubt on this consensus. Genomic sequencing has revealed many new examples of balanced polymorphisms, and genome-wide scans for balancing selection have uncovered hundreds of additional candidates (see Section IV.1). Although these candidates require further validation, the current list likely represents the tip of the iceberg, given that genomic methods for inferring balancing selection are often under-powered and rely on long-term signals (Fijarczyk & Babik, 2015; Bitarello *et al.*, 2023). Second, arguments about genetic loads have become less relevant to contemporary debates about balancing selection because molecular genetic diversity is now thought to be predominantly neutral or mildly deleterious (Leffler *et al.*, 2012;

Jensen *et al.*, 2019). The focus has instead shifted to the role of balancing selection in maintaining the extensive genetic variation for life-history traits and other fitness components, which is indeed too high to be explained by mutation alone (Charlesworth & Hughes, 2000; Charlesworth, 2015; Sharp & Agrawal, 2018; Bonnet *et al.*, 2022). Finally, new developments in theoretical modelling of adaptation give prominence to balancing selection. While earlier models emphasised the often-restrictive conditions for long-term balancing selection, newer models have highlighted the potential for short-lived episodes of balancing selection during the evolution of traits towards their optimum (Manna, Martin & Lenormand, 2011; Sellis *et al.*, 2011; Connallon & Clark, 2014). Moreover, a surge in theoretical models of fluctuating selection – inspired by recent evidence of predictable seasonal fluctuations of nucleotide polymorphism (Bergland *et al.*, 2014; Machado *et al.*, 2021; Rudman *et al.*, 2022; Johnson *et al.*, 2023) – has highlighted broader conditions for balancing selection than implied by classical models (Wittmann *et al.*, 2017; Bertram & Masel, 2019; Johnson *et al.*, 2023; Yamamichi, Ellner & Hairston, 2023).

The renewed interest in balancing selection has prompted several reviews of empirical progress in detecting it (Fijarczyk & Babik, 2015; Bitarello *et al.*, 2023), but a review of the underlying population genetic *theories* of balancing selection is lacking. Here, we present a comprehensive and accessible overview of this theory. As is true for most models, the devil is in the details, and a deeper understanding requires some engagement with the particulars. We therefore provide a largely verbal overview in the main text, collect technical aspects in the figure and table legends, and elaborate further in mathematical derivations presented in the online Supporting Information.

We begin our review with the idealised conditions that characterise the very first models of balancing selection: i.e. single biallelic genetic loci evolving in large, randomly mating, diploid populations (Fig. 1). These conditions mirror Fisher's (1922) classic analysis of heterozygote advantage (Charlesworth, 2022a). As the 20th century progressed, the major technical innovations and debates that stimulated empirical evolutionary biology (e.g. allozyme and genomic data, the neutral theory debate; Fig. 1) coincided with the development of theories of balancing selection. We therefore examine how key aspects of biological complexity were gradually incorporated into the theory (Fig. 1), namely: non-random mating, deviations from diploidy, genetic drift, linkage and recombination between loci, and different forms of trait inheritance and phenotypic selection. We close by outlining progress in linking theoretical predictions about balancing selection to empirical data.

II. MODELS OF BALANCING SELECTION: THE BASICS

(1) The concept of balancing selection

Balancing selection occurs when natural selection, without the intervention of other processes such as genetic drift, mutation, or migration, maintains genetic polymorphism. It can arise from a variety of specific scenarios (Table 1), but in all scenarios rare alleles have an evolutionary advantage over common alleles. This aligns with the intuition that balancing selection maintains variation by opposing the loss of rare variants, as well as its operational definition of 'protected polymorphism' in mathematical population genetics (Prout, 1968). In the models outlined in Table 1, balancing selection occurs when the A_1 allele (with frequency p) is favoured at frequencies near $p = 0$, and the A_2 allele (with frequency $q = 1 - p$) is favoured at frequencies near $p = 1$. In other words, it occurs when both boundary equilibria ($p = 0$ and $p = 1$) are 'unstable'. Conditions leading to this consistent rare-allele advantage ('protected polymorphism'; Prout, 1968) are determined by stability analysis of the boundary equilibria (see chapter 5 in Otto & Day, 2007).

Still, this definition is easy to misinterpret, and we outline several common misconceptions in Table 2.

(2) Scenarios of balancing selection

Consider an idealised model in which a single genetic locus segregates for two alleles, the population is infinitely large and diploid, mating is random, and generations are discrete (as in Table 1). One scenario that generates balancing selection under these assumptions is heterozygote advantage (i.e. overdominance), in which heterozygotes have higher fitness (i.e. higher survival and/or fertility) than homozygotes (Fig. 2A) (Fisher, 1922; Hedrick, 2012). Each allele, when rare, is expected to increase in frequency because rare variants are predominantly found in (fit) heterozygotes, whereas common variants are mostly found in (less-fit) homozygotes. Although the fitness of each genotype is independent of its frequency, the average fitness of each *allele* – its so-called 'marginal fitness' – declines as the allele's frequency increases (Fig. 2B). Under heterozygote advantage, the population evolves towards a polymorphic equilibrium at which the marginal fitness of both alleles is equal (Fig. 2B, C). Heterozygote advantage can also maintain more than two alleles at a single locus, although conditions for maintenance of many alleles become restrictive unless there is a high degree of symmetry among homozygous and heterozygous genotypes for the set of alleles (Lewontin, Ginzburg & Tuljapurkar, 1978; Charlesworth & Charlesworth, 2010), or unless populations evolve towards conditions where maintaining many alleles becomes permissive (Marks & Spencer, 1991; Waxman & Gavrilets, 2005).

Balancing selection is also likely, although not inevitable, when the fitness of each *genotype* declines with its frequency in the population – a scenario referred to as negative frequency-dependent selection (Haldane & Jayakar, 1963a; Ayala & Campbell, 1974). In such cases, rare genotypes may consistently experience fitness advantages over more common ones. There is a vast ecological literature on negative frequency-dependent selection (Gómez-Llano *et al.*, 2024) and myriad ways to model it (see chapter 5 of Wright, 1969; Lande, 1976;

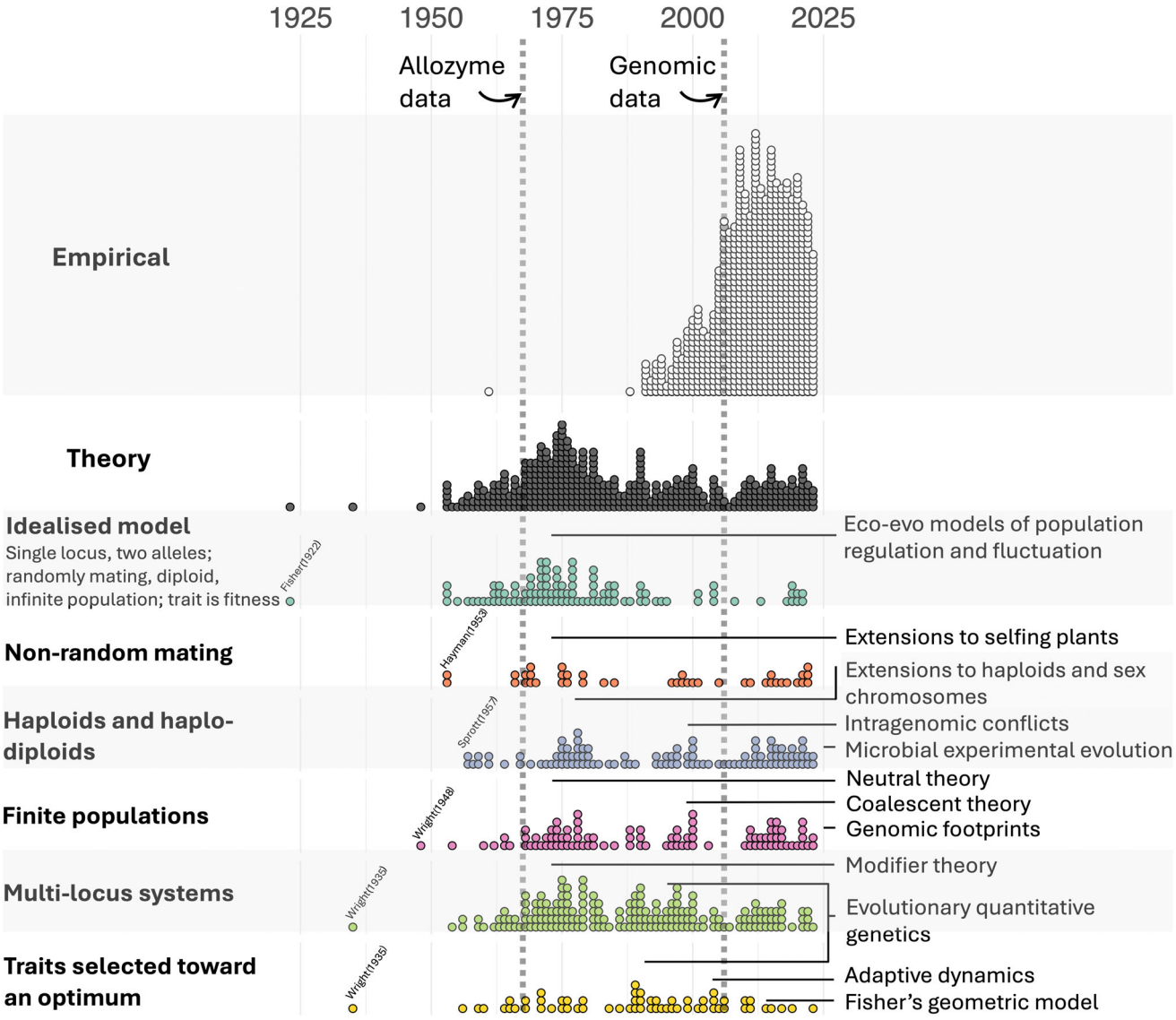

Fig. 1. Timeline of balancing selection theory and data. Each dot represents a paper on balancing selection. Papers were identified by a targeted search of the *Web of Science*, followed by manual curation of theory papers missed by the search ($N = 872$ empirical papers, $N = 402$ theory papers; see Data S1 and S2 for the full bibliography). The top panel illustrates empirical research on balancing selection, which grew dramatically in the 1980s, spurred by the discovery of sequence variants (protein polymorphisms termed allozymes) and DNA variants, including molecular markers (e.g. microsatellites) and, later, genome sequences. The next panel illustrates the gradual growth of balancing selection theory, which spiked in the mid-1970s, spurred by the debate over neutral theory and a desire to account for abundant protein polymorphisms in natural populations (Lewontin & Hubby, 1966; Lewontin, 1974; Gillespie & Langley, 1974; Clarke, 1979), and has gained ground in the genome era (2010s). The bottom panels separate the theoretical papers into those that follow an 'idealised model' (described in Section II), and those that consider different aspects of biological complexity (described in Section III). Individual theory papers can span multiple aspects of complexity at once. The lines (right) highlight some particularly influential developments in the theory. The labelled studies (left) indicate the first studies published for each aspect of complexity.

Golding, 1992). For example, models of coevolution between interacting host and parasite species can generate balancing selection through negative frequency dependence (Haldane, 1949; Brown & Tellier, 2011; MacPherson, Keeling & Otto, 2021). In Table 1, we present a simple illustrative example of negative frequency dependence that can either lead to balancing selection, or to fixation of one allele and extinction of the other (i.e. to 'directional selection'; see Appendix S1).

Balancing selection can also arise from a variety of genetic trade-offs, in which alleles that are advantageous in some contexts are harmful in others (Table 1). In the case of

Table 1. Single-locus models of balancing selection. We outline several scenarios that can lead to balancing selection, including heterozygote advantage, negative frequency-dependent selection with multiplicative interactions between alleles, meiotic drive, and a trade-off model that can be applied to sexual antagonism, niche antagonism, and antagonistic pleiotropy (see Appendix S1 for criteria for balancing selection under each scenario). s_1, s_2 and s represent homozygous fitness costs (i.e. selection coefficients) of an allele, h_1, h_2 and h represent dominance coefficients, and p represents the frequency of the A_1 allele. Selection coefficients are positive quantities that cannot exceed 1 (because fitness values cannot be negative), while dominance coefficients can range from partial-to-complete recessivity ($0 \leq h < 0.5$), to co-dominance (*i.e.* $h = h_1 = h_2 = 0.5$), to partial-to-complete dominance ($0.5 < h \leq 1$). The strength of meiotic drive, i.e. transmission advantage (c, where $0 \leq c \leq 1$), is scaled so that $c = 0$ corresponds to standard Mendelian segregation and $c = 1$ to 100% transmission of the drive allele.

	A_1A_1	A_1A_2	A_2A_2
Heterozygote advantage	$1-s_1$	1	$1-s_2$
Negative frequency-dependent selection	$(1-s_1 p)^2$	$(1-s_1 p)(1-s_2)$	$(1-s_2)^2$
Meiotic drive			
Fitness of carrier	$1-s$	$1-sh$	1
A_2 transmission	1	$(1+c)/2$	0
Trade-off			
Fitness context 1	1	$1-s_1 h_1$	$1-s_1$
Fitness context 2	$1-s_2$	$1-s_2 h_2$	1
Average fitness	$1-\frac{s_2}{2}$	$1-\frac{s_1 h_1 + s_2 h_2}{2}$	$1-\frac{s_1}{2}$

Table 2. Clarifying misconceptions about balancing selection. We list some possible misconceptions (left) and our attempts to clarify these (right).

Misconception	Explanation
It is a category of trait selection	Natural selection refers to the differential fitness of individuals expressing different *phenotypes*, which can occur regardless of the genetic basis of the trait in question. By contrast, balancing selection refers to the *genetic consequences* of natural selection, i.e. it is any form of selection that maintains genetic polymorphism at one or more loci (Table 1). Thus, no single form of trait selection (e.g. directional, disruptive, or stabilising; Kingsolver *et al.*, 2001) necessarily generates balancing selection at trait-affecting loci (Turelli & Barton, 2004; Bürger & Gimelfarb, 2004).
It is equivalent to heterozygote advantage, negative frequency-dependent selection on genotypes, or trade-offs	Each of these scenarios can generate balancing selection, but they need not. For example, heterozygote advantage does not always lead to balancing selection (see Fig. 4), nor do models of negative frequency-dependent selection (see chapter 2 of Felsenstein, 2019) or trade-offs (see Fig. 3). While balancing selection implies that the 'marginal fitness' of each *allele* declines with its frequency (Fig. 2B), it does not imply that the fitness of each *genotype* declines with its frequency (Table 1).
It is always a long-term process	Balancing selection is often used interchangeably with long-term balancing selection (i.e. of duration longer than $4N_e$ generations, where N_e is the effective population size; Bitarello *et al.*, 2023), possibly because genome scans often rely on long-term signals, or because the term 'stability' is taken to imply perpetual stability of a balanced polymorphism. However, timescale is not part of the definition of balancing selection. It can be transient (e.g. over relatively few generations) or persistent (e.g. over many thousands of generations), with each scenario leaving a different genomic footprint.
It should always elevate polymorphism in real populations	When drift is strong relative to selection, balancing selection can lead to patterns of polymorphism that are indistinguishable from neutrality, both at the target of selection or at linked loci. Balancing selection combined with drift can even *reduce* levels of genetic diversity, relative to neutrality, when the equilibrium frequency of one of the selected alleles is close to zero (see Section III.3).
It is the only evolutionary process that 'maintains' genetic polymorphism	Balancing selection maintains polymorphism in the absence of other evolutionary factors. However, interactions among mutation, migration, genetic drift, and positive or purifying selection are also capable of maintaining polymorphism (Haldane, 1930, 1937; Charlesworth & Charlesworth, 2010). For example, purifying selection against harmful genetic variants is offset by mutation, which continuously introduces new harmful variants. Genetic variation can then be maintained at the equilibrium between these two opposing processes ('mutation–selection balance').

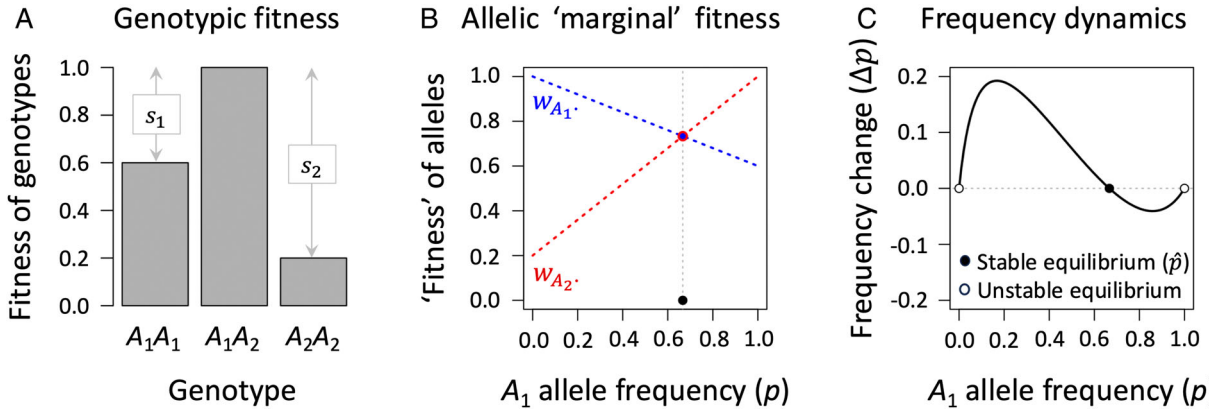

Fig. 2. Heterozygote advantage as an example of balancing selection. (A) For a locus with two alleles (A_1 and A_2, at frequencies p and q), the fitness of A_1A_1 homozygotes declines by s_1 ($w_{A_1A_1} = 1 - s_1$) and that of A_2A_2 declines by s_2 ($w_{A_2A_2} = 1 - s_2$), relative to heterozygotes ($w_{A_1A_2} = 1$). (B) Although fitness per genotype is frequency-*in*dependent, the average transmission rate of each allele to the next generation (its 'marginal fitness') is frequency dependent. In outbred, randomly mating populations, the marginal fitness of each allele ($w_{A_1\cdot} = pw_{A_1A_1} + qw_{A_1A_2} = 1 - ps_1$ and $w_{A_2\cdot} = pw_{A_1A_2} + qw_{A_2A_2} = 1 - qs_2$) is negatively frequency-dependent (the marginal fitness of each allele declines as its frequency increases), becoming equal at the polymorphic equilibrium $\hat{p} = s_2/(s_1 + s_2)$ (marked by the filled circle). (C) Whether the A_1 allele increases ($\Delta p > 0$) or decreases in frequency ($\Delta p < 0$) depends on its current frequency relative to the equilibrium.

meiotic drive, a 'driver' allele has a transmission advantage because it finds itself in more than half of the gametes produced by heterozygotes. However, driver alleles may also lower the fitness of individuals that carry them (Prout, 1953; Rode *et al.*, 2019). The trade-off between an allele's transmission advantage and its fitness cost to carriers can potentially generate balancing selection. Trade-offs can also arise between temporally fluctuating environmental conditions (Wright, 1948; Dempster, 1955; Haldane & Jayakar, 1963b; Wittmann *et al.*, 2017; Bertram & Masel, 2019; Johnson *et al.*, 2023; Yamamichi *et al.*, 2023), different resources or 'niches' used by the population ('niche antagonism', NA) (Levene, 1953; Christiansen, 1975; Felsenstein, 1976; Hedrick, 2006), females and males ('sexually antagonistic selection', SA) (Owen, 1953; Kidwell *et al.*, 1977; Bonduriansky & Chenoweth, 2009), and life-history traits ['antagonistic pleiotropy' (AP) between e.g. survival and fertility] (Rose, 1982; Curtsinger, Service & Prout, 1994).

In each trade-off model, the balance between benefits and costs must be just right to maintain the polymorphism (Fig. 3), and conditions leading to directional selection are often more permissive than those leading to balancing selection (Maynard Smith & Hoekstra, 1980; Prout, 2000). Conditions for balancing selection are particularly restrictive when selection is weak (as we often expect it to be) and the benefits and costs associated with each allele have similar degrees of dominance (Fig. 3). However, conditions for balancing selection become much more permissive when the cost of expressing each allele is at least partially recessive while its benefit is dominant. Such 'favourable reversals of dominance' or 'dominance reversals' (Gillespie & Langley, 1974; Charlesworth & Charlesworth, 2010; Fry, 2010; Connallon & Chenoweth, 2019; Reid, 2022; Grieshop, Ho & Kasimatis, 2024) fortuitously elevate the expression of beneficial effects of trade-off alleles while hiding their harmful effects, which increases the likelihood that the average fitness of heterozygotes, which carry different trade-off alleles, is greater than the average fitness of homozygotes for the alleles. This 'net heterozygote advantage' is a sufficient condition for balancing selection in randomly mating diploid populations (e.g. in Table 1, complete dominance reversal, where $h_1 = h_2 = 0$, generates a net heterozygote advantage and balancing selection across the entire parameter space of s_1 and s_2). A net heterozygote advantage is necessary for balancing selection through AP (Curtsinger *et al.*, 1994), but not under SA or NA, where co-dominant benefits and costs do not lead to a net heterozygote advantage but permit balancing selection (Kidwell *et al.*, 1977; Connallon & Chenoweth, 2019).

In addition to dominance reversals, conditions for balancing selection in NA models can expand when there are barriers to mixing between habitats [e.g. due to geographic isolation or habitat choice (Smith, 1970; Bulmer, 1972)], rather than full mixing of adults during mating (as assumed in Table 1; see Appendix S1 for broader mathematical criteria). However, scenarios with restricted migration stretch the definition of balancing selection, since the maintenance of variation now reflects the balance between local selection, which favours the fixation of locally beneficial alleles, and gene flow, which continually introduces locally maladaptive alleles into each subpopulation (see chapter 4 of Charlesworth & Charlesworth, 2010; Hereford, 2009; Fan *et al.*, 2016). This 'migration–selection balance' mechanism is an important but distinct mechanism for maintaining variation, alongside balancing selection and mutation–selection balance (Table 2).

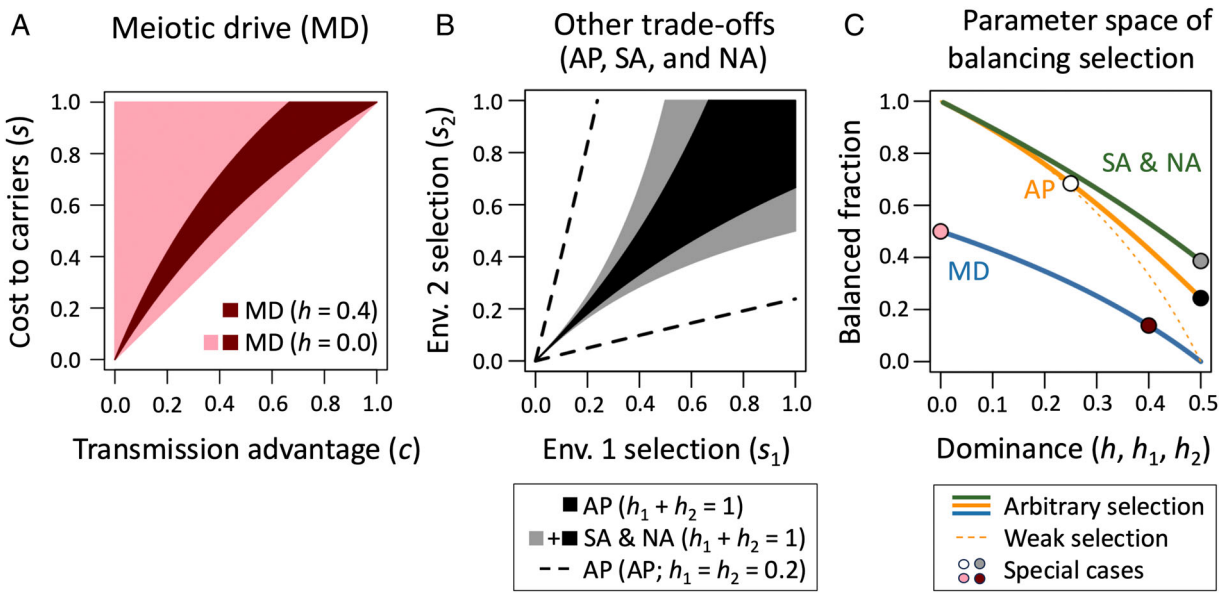

Fig. 3. Dominance and opportunities for balancing selection through trade-offs. Conditions for balancing selection (with parameters defined in Table 1) under trade-off scenarios where a polymorphic equilibrium is attainable, i.e. meiotic drive (MD), antagonistic pleiotropy (AP), sexually antagonistic selection (SA), and niche antagonism (NA). Balancing selection is possible under MD (shaded regions of panel A; Rode *et al.*, 2019) when the homozygous fitness cost (selection coefficient, s) of a drive allele to its carriers is greater than the transmission advantage (c), and the cost is at least partially recessive (dominance coefficient $h < 0.5$). Other trade-off scenarios can generate balancing selection when fitness costs are co-dominant on average (h_1, $h_2 = 0.5$, shaded regions of B; Maynard Smith & Hoekstra, 1980; Connallon & Chenoweth, 2019), although conditions are restrictive unless selection is strong. Conditions become much more permissive when the expression of each allele is recessive in contexts where it is costly, and dominant in contexts where it is beneficial (C illustrates how greater masking of fitness costs, i.e. smaller values of h, h_1, and h_2, expands the parameter space leading to balancing selection). Note that the NA model consists of two equally sized ecological niches with random dispersal and 'soft selection', which is a special case of Levene's more general model (Levene, 1953; Christiansen, 1975).

(3) Allele frequency dynamics under balancing selection

Although the details of individual balancing selection scenarios vary, their allele frequency dynamics often simplify to a common form that highlights their conceptual unity. For models with a single polymorphic equilibrium, allele frequency change per generation is approximately:

$$\Delta p \approx \alpha pq\left(\widehat{p}-p\right) \tag{1}$$

where p and $q = 1 - p$ refer to A_1 and A_2 allele frequencies, α is the net strength of selection (here assumed to be weak, such that $|\alpha| \ll 1$), and $\widehat{p}$ is the polymorphic equilibrium. Under balancing selection, $\alpha > 0$ and $0 < \widehat{p} < 1$, with values of α and $\widehat{p}$ depending on the scenario of balancing selection and its underlying parameters. For example, with heterozygote advantage, $\alpha = s_1 + s_2$ and $\widehat{p} = s_2/(s_1 + s_2)$ (expressions for α and $\widehat{p}$ for the other scenarios can be found in Appendix S1).

Several insights emerge from Equation (1). First and most obviously, evolutionary change requires genetic variation at the locus ($0 < pq < 1$). Second, given that αpq must be positive when genetic variation is present, the term $\left(\widehat{p}-p\right)$ determines the direction of evolutionary change. The frequency of A_1 increases when it is below the equilibrium, decreases when it is above the equilibrium, and remains stable at the equilibrium. Therefore, in the absence of genetic drift, balancing selection causes a genetically variable population to evolve towards the polymorphic equilibrium. This is illustrated in Fig. 2C for the case of heterozygote advantage, although similar dynamics characterise each of the scenarios outlined in Table 1.

While most models of balancing selection can be recast in the form described by Equation (1), there are notable exceptions. For example, temporal fluctuations in the direction of selection can maintain polymorphism (Haldane & Jayakar, 1963b; Lande, 2007; Wittmann *et al.*, 2017), but there is no stable polymorphic equilibrium and the population instead cycles through a range of polymorphic allele frequency states (see also Chevin, Gompert & Nosil, 2022). In models with multiple alleles (Lewontin *et al.*, 1978; Spencer & Marks, 1988), the frequency dynamics of each allele usually depend on all other alleles instead of just being proportional to $p(1-p)$. This is true of self-incompatibility systems, which can stably maintain many different alleles at a single locus, and also favour new alleles that may arise (Nagylaki, 1975; Constable & Kokko, 2018; Czuppon & Constable, 2019; Czuppon & Billiard, 2022), or in rock–

paper–scissors games, where type A outperforms B, B outperforms C, and C outperforms A (Sinervo & Lively, 1996). Lastly, Equation (1) cannot accommodate models with multiple polymorphic equilibria (Owen, 1953; Kidwell *et al.*, 1977), or models with non-linear frequency-dependent selection, such as game theory models involving interactions between more than two individuals (Hofbauer & Sigmund, 1998; Leimar & McNamara, 2023).

III. ADDING BIOLOGICAL COMPLEXITY TO MODELS OF BALANCING SELECTION

All models are simplifications, and the scenarios of balancing selection presented above obviously omit important aspects of biological complexity. In some cases, violations of their simplifying assumptions can fundamentally alter opportunities for balancing selection, or the evolutionary stability of balanced polymorphisms. For example, while many populations are indeed diploid and mate nearly randomly at most loci, others – such as haplo-diploid species, or self-fertilising plants – are not. Conditions for balancing selection that go beyond the diploid and randomly mating ideal were increasingly explored during the second half of the 20th century (Hayman, 1953; Sprott, 1957) (Fig. 1). Likewise, while models that ignore genetic drift are often useful approximations of reality, drift is an inevitable feature of real populations with the potential to destabilise balanced polymorphisms (Robertson, 1962). The rise of the neutral theory of molecular evolution (Kimura, 1983), coalescent theory (Kingman, 1982), along with the increasing feasibility of computer simulations, led to a burst of finite-population models of balancing selection (Cook & Hartl, 1975; Hedrick, 1976; Gillespie, 1978, 1997; Kaplan, Darden & Hudson, 1988) (Fig. 1). Finally, while single-locus models may well describe traits with a simple genetic basis (i.e. whose expression is dictated by few genetic variants), they apply awkwardly to continuous traits. The advent of models of multi-locus genetic systems (Bodmer & Felsenstein, 1967; Karlin, 1975), and various models that link genotype, phenotype and fitness (Bulmer, 1971; Gillespie, 1984; Geritz & Kisdi, 2000; Turelli & Barton, 2004; Sellis *et al.*, 2011), extended the scope of theories of balancing selection beyond single loci (Fig. 1). We outline the consequences of each of these aspects of biological complexity below.

(1) Non-random mating

Mating patterns influence the proportion of heterozygotes and, thereby, opportunities for balancing selection in scenarios where heterozygotes are favoured over homozygotes (i.e. in cases involving true or net heterozygote advantage; see Figs 2 and 3). Mating patterns that decrease the proportion of heterozygotes (e.g. inbreeding or positive assortative mating by genotype) tend to decrease the range of conditions leading to balancing selection (Hayman, 1953; Glémin, 2021), while mating patterns that increase the proportion of heterozygotes (e.g. disassortative mating by genotype) tend to do the opposite (Arnqvist, 2011; Kasimatis, Ralph & Phillips, 2019).

Consider the widespread case of inbreeding, which reduces heterozygote proportions relative to random mating. Models of balancing selection with inbreeding can be expressed using Equation (1), but with parameters α and $\widehat{p}$ adjusted to include the population's inbreeding coefficient (F) where $F=1$ denotes complete inbreeding and $F=0$ denotes complete outcrossing. Under weak heterozygote advantage, the net strength of selection becomes $\alpha=(1-F)(s_1+s_2)$, the polymorphic equilibrium is $\widehat{p}=(s_2-Fs_1)/\alpha$, and balancing selection arises when $Fs_1<s_2<s_1/F$ (see equations 14 and 15 in Glémin, 2021). Thus, inbreeding decreases the parameter range for balancing selection by a factor of $1-F$ when selection is weak (Fig. 4A), and somewhat less when selection is strong (Kimura & Ohta, 1971). Inbreeding also depresses the scope of balancing selection resulting from trade-offs (Hayman, 1953; Hedrick, 1998; Glémin, 2010, 2021; Jordan & Connallon, 2014). This can arise when there is net heterozygote advantage (e.g. SA selection with dominance reversal; Tazzyman & Abbott, 2015), or when self-fertilisation reduces the strength of selection through the male sex function of hermaphrodites, which promotes the fixation of SA alleles that benefit females (Jordan & Connallon, 2014; Olito, 2017; Glémin, 2021). By contrast, inbreeding has little effect on balancing selection arising from negative frequency-dependent selection (Anderson, 1969; Glémin, 2021).

Even when balancing selection is predicted to occur, inbreeding reduces the effective size of the population (Charlesworth, 2009) and increases selective interference between genetically linked loci (Hartfield, Bataillon & Glémin, 2017). This promotes the loss of polymorphism by reducing the efficacy of balancing selection relative to genetic drift (Glémin, 2021) (see Section III.3). On the other hand, inbreeding can sometimes facilitate balancing selection of multi-locus allele combinations (Olito, 2017) and intensify population genomic signals of long-term balancing selection (Nordborg, Charlesworth & Charlesworth, 1996; Wiuf *et al.*, 2004).

(2) Haploids and haplo-diploids

Even if heterozygotes have higher fitness than homozygotes, such advantages become irrelevant in predominantly haploid populations, haploid individuals, or haploid stages of a life cycle (i.e. gametes or the gametophyte stage of plants). In fully haploid populations, there is no scope for balancing selection by heterozygote advantage, meiotic drive (MD), or AP. Balancing selection may still arise from negative frequency-dependent selection (Smouse, 1976; Svensson & Connallon, 2019) or from trade-offs between niches, seasons or sexes (Gliddon & Strobeck, 1975; Czochor & Leonard, 1982; Dean, 2005; Débarre & Gandon, 2011). However, the conditions for balancing selection under such

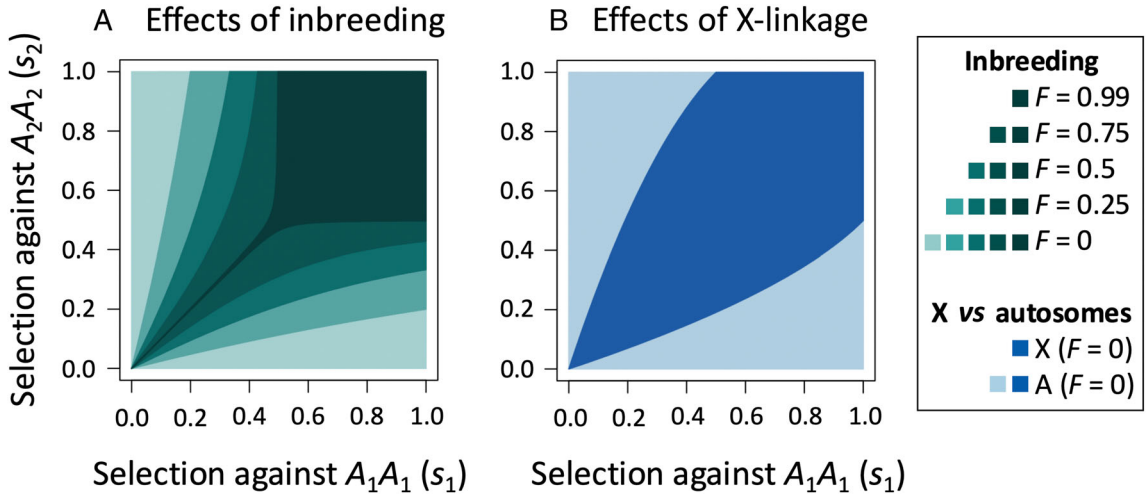

Fig. 4. Consequences of inbreeding and X-linked (or haplo-diploid) inheritance on heterozygote advantage. Whereas outbred and diploid populations can maintain a balanced polymorphism over the entire parameter space of selection (the full range of values for the selection coefficients s_1 and s_2; $0<s_1, s_2 \leq 1$), inbred diploid populations (A) and X-linked genes or haplo-diploid populations (B) reduce the parameter space for balanced polymorphism (dark shaded regions). Results are based on exact criteria for balancing selection (Pamilo, 1979; Rocheleau & Lessard, 2000). F is the inbreeding coefficient, where $F=1$ denotes complete inbreeding and $F=0$ denotes complete outcrossing.

trade-offs are highly restrictive. In the case of trade-offs between sexes or niches, conditions for balancing selection under haploidy are equivalent to those under diploidy with co-dominance (Fig. 3).

When populations experience selection in both diploid and haploid life stages, or when diploid and haploid individuals co-exist, conditions for balancing selection are often intermediate between purely diploid and haploid populations (Pamilo, 1979). For example, at loci where one sex is haploid and the other is diploid (e.g. haplo-diploids, X-linked genes that are hemizygous in males), heterozygote advantage in the diploid context favours the maintenance of polymorphism, while the haploid context typically favours its loss. Hence, balancing selection only occurs when heterozygote advantage in the diploids outweighs directional selection in the haploids (as in the dark-shaded region of Fig. 4B, where s_1 and s_2 have similar magnitudes, implying weak directional selection in haploids). In the rest of the parameter space, the allele that is least harmful in homozygous or haploid individuals is fixed (light-shaded regions of Fig. 4B). Conditions for X-linked balancing selection are also reduced in models involving AP, trade-offs between niches (NA), and MD occurring in females (see Appendix S2; Moody, 1979).

Although X-linked inheritance usually restricts conditions for balancing selection, exceptions can occur. Cases of male meiotic drive are especially complex because they are associated with skewed sex ratios, altered population size dynamics, and potentially extinction (Edwards, 1961; Hamilton, 1967; Mackintosh, Pomiankowski & Scott, 2021). In models of SA selection (Rice, 1984; Patten & Haig, 2009; Fry, 2010), the sex-specific dominance coefficients of the alleles determine whether polymorphisms are more readily maintained at autosomal (diploid) or X-linked loci. Specifically, the X is more permissive for balancing selection when male fitness costs of SA alleles show moderate to strong dominance ($h_m > 1/(2 - s_m)$, where h_m and s_m represent male dominance and selection coefficients), but autosomes are more permissive otherwise (Ruzicka & Connallon, 2020). Comparable results arise under 'ploidally antagonistic selection', where different alleles are favoured in the haploid and diploid stages of a life cycle (Immler, Arnqvist & Otto, 2012), and where criteria for balancing selection can sometimes expand (Immler *et al.*, 2012).

(3) Finite populations

Real populations are finite and subject to genetic drift, which causes random deviations from deterministic evolutionary trajectories. Despite this randomness, population genetic models generate clear predictions for the 'stationary' (i.e. long-run) probability of observing each possible allele frequency state, as a function of the effective population size (N_e) and the specific scenario of balancing selection (Fig. 5A). For the scenarios in Table 1, the stationary distribution for the A_1 allele [a special case of Wright's (1945) distribution] is:

$$\psi(p) = C[p(1-p)]^{2kN_e u - 1} e^{-kN_e \alpha \left(\widehat{p} - p\right)^2} \qquad (2)$$

where α is the net strength of selection (assumed to be weak), k is the number of gene copies carried by each member of the population ($k=2$ for diploids and $k=1$ for haploids), u is the mutation rate per locus (assumed to be the same for each allele), and C is a constant that ensures that the distribution integrates to one (i.e. $1/C = \int_0^1 [p(1-p)]^{2kN_e u - 1} e^{-kN_e \alpha \left(\widehat{p} - p\right)^2} dp$)

[see Appendix S3; Robertson (1962) provides an early application of Wright's model to a balancing selection scenario].

Analyses of the stationary distribution reveal two important consequences of drift for polymorphisms under balancing selection. First, given no additional mutations entering the population, a balanced polymorphism will eventually be lost despite selection to maintain it (see p. 165 of Ewens, 2004). Second, and somewhat counterintuitively, drift can sometimes lead to more rapid loss of a balanced polymorphism than a neutral polymorphism (Robertson, 1962; Connallon & Clark, 2012; Mullon, Pomiankowski & Reuter, 2012), resulting in lower genetic diversity than expected at neutrally evolving loci (Fig. 5B). The effect arises because one of the alleles is maintained at a low frequency by balancing selection, where it is dangerously close to extinction and loss of the polymorphism becomes likely (for elaboration on this effect, see Appendix S3). This outcome is particularly likely when the population-scaled strength of selection is small (e.g. $kN_e\alpha<10$) and equilibrium allele frequencies are close to 0 or 1 (Carr & Nassar, 1970; Ewens & Thomson, 1970; Nei & Roychoudhury, 1973).

These counterintuitive predictions for balancing selection in finite populations can be viewed as a special case of a broader population genetic phenomenon. Intuition might lead us to predict that loci under balancing selection should exhibit the highest levels of genetic diversity, followed by neutral loci, followed by loci under positive or purifying selection. The classic theory clearly shows that balanced polymorphisms can harbour more or less diversity than neutral loci (Fig. 5B), mirroring results of recent models of genetic diversity for loci under weak positive selection (Mafessoni & Lachmann, 2015; Charlesworth, 2022b). Thus, there is no one-to-one mapping between balancing selection and inflation of genetic diversity relative to neutral expectations.

(4) Multi-locus systems with linkage

The models discussed so far have considered single loci, yet genes can mutually influence each other's potential for generating balancing selection when they are genetically linked on a chromosome. Most analyses have focused on conditions that maintain polymorphism at a pair of partially linked, biallelic loci (Karlin, 1975). In the case of heterozygote advantage, polymorphism can be maintained at linked loci (Bodmer & Felsenstein, 1967; Feldman, Franklin & Thomson, 1974). In trade-off scenarios, linkage tends to expand conditions for the maintenance of polymorphism relative to single-locus models (Gregorius, 1991). For example, a haploid two-locus system can favour a balanced polymorphism in a temporally fluctuating environment (Kirzhner, Korol & Ronin, 1995; Novak & Barton, 2017), whereas this is less likely to occur in single-locus models (Haldane & Jayakar, 1963b; Nagylaki, 1975; Dean, 2005). Conditions for polymorphism also expand under restricted recombination in scenarios of niche and sexual antagonism (Bürger, 2009; Patten, Haig & Úbeda, 2010; Arnqvist, Vellnow & Rowe, 2014; Patten, 2014; Olito, 2017), though the opposite is true for AP (Curtsinger *et al.*, 1994).

Even if loci are not individually under balancing selection, co-inherited blocks of alleles ('haplotypes') can be maintained under balancing selection. This can occur if each haplotype becomes fixed for different partially recessive deleterious mutations that are strongly expressed in homozygotes of each haplotype, but strongly masked in heterozygotes (Sturtevant & Mather, 1938; Charlesworth, 2024). The

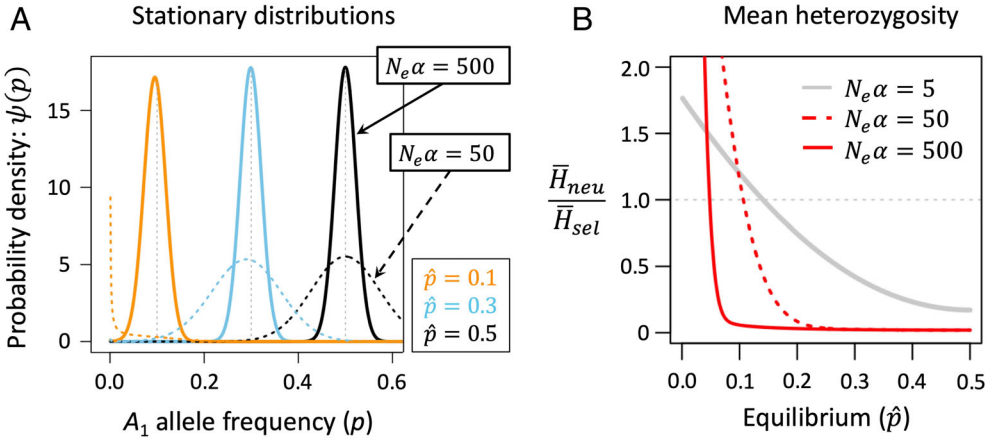

Fig. 5. Interactions between balancing selection and genetic drift. (A) Diffusion approximations are used to predict stationary (long-term) distributions (Equation (2)) for three equilibrium frequency states ($\hat{p}$), and two population-scaled strengths of selection ($N_e\alpha$), where N_e is the effective population size and α is the net strength of selection. (B) The ratio of mean genetic (e.g. nucleotide) diversity for neutral loci relative to loci under balancing selection. For each parameter combination, the expected heterozygosity ($\overline{H}$) is numerically calculated as $\overline{H}=\int 2p(1-p)\psi(p)dp$, where $2p(1-p)$ is the heterozygosity and $\psi(p)$ is the stationary distribution. When the ratio is greater than 1, then expected heterozygosity under neutrality ($\overline{H}_{neu}$) is higher than under balancing selection ($\overline{H}_{sel}$). Results for both panels assume $2kN_eu=0.01$ and $k=2$ (diploidy).

resulting pattern of 'pseudo-overdominance' can maintain both haplotypes, provided they do not recombine to produce mutation-free genetic combinations (Ohta & Kimura, 1969; Waller, 2021; Abu-Awad & Waller, 2023). For example, pseudo-overdominance might contribute to the maintenance of polymorphic chromosomal inversions (Faria *et al.*, 2019; Jay *et al.*, 2021; Berdan *et al.*, 2021), either when new inversions capture combinations of beneficial and deleterious recessive alleles and subsequently spread to an intermediate frequency (Kirkpatrick & Barton, 2006; Connallon & Olito, 2022), or when recessive deleterious mutations accumulate on inversions that are already common within the population (Charlesworth, 2024).

Finally, balancing selection can also maintain allelic diversity at *neutral* sites that are linked to a balanced polymorphism (Kelly & Wade, 2000; Khudiakova, Barton & Arnqvist, 2025), also known as 'associative overdominance' [Note that the term can also refer maintenance of neutral alleles that are tightly linked to partially recessive deleterious alleles (Ohta, 1971); see pp. 403–404 of Charlesworth & Charlesworth (2010)]. In cases of heterozygote advantage (Ohta & Kimura, 1970), associative overdominance maintains neutral polymorphism when the recombination rate between neutral and selected loci is smaller than the strength of selection (Zhao & Charlesworth, 2016). The diversity at neutral sites increases with the number of balanced polymorphisms they are linked to (Navarro & Barton, 2002) – a prediction that applies to various scenarios, including heterozygote advantage (Kaplan *et al.*, 1988), and temporally fluctuating selection (Wittmann, Mousset & Hermisson, 2023). And, just as balancing selection can sometimes *reduce* diversity at the selected site relative to neutrality (Fig. 5B), this diversity-reducing effect can extend to linked neutral loci as well (Wittmann *et al.*, 2023).

(5) Traits selected towards an optimum

The models described so far do not explicitly include phenotypic effects; instead, genotypes are assigned fitness values that indirectly reflect selection on phenotypes. However, the lack of a genotype–phenotype map limits the range of questions we can ask about balancing selection. How often should we expect balancing selection to arise among new mutations or segregating genetic variants? Should we expect balanced polymorphisms to be transiently or persistently maintained over time? While the 'parameter space' for balancing selection (Figs 3 and 4) might seem, at first glance, a reasonable proxy for the likelihood of maintaining variation under a given scenario – or a framework for comparing scenarios – it does not differentiate between biologically plausible *versus* implausible parameter values. We therefore need models that specify the mapping between genotype, phenotype and fitness.

A common way to predict the prevalence of balancing selection is to model the fitness effects of mutations affecting traits selected towards an optimum (Turelli & Barton, 2004; Waxman & Gavrilets, 2005; Sellis *et al.*, 2011). For example, studies using Fisher's geometric model (Fisher, 1930) usually examine trait systems in which adaptive mutations are sufficiently rare that adaptation proceeds by a temporal series of evolutionary steps ('adaptive walks'), with each step corresponding to the invasion of a new adaptive variant (McCandlish & Stoltzfus, 2014; chapter 27 of Walsh & Lynch, 2018). These mutation-limited dynamics of adaptation are most relevant to trait systems with small mutational targets, or where the mutations' 'scaled' phenotypic effect sizes are large, which limits the availability of adaptive mutations (Fig. 6). Importantly, *scaled* sizes can be large even if *absolute* phenotypic effect sizes of mutations are small, provided the population is near its optimum and/or the number of pleiotropically associated traits under selection (i.e. phenotypic dimensionality or 'complexity') is high (Fisher, 1930; Orr, 1998; Manna *et al.*, 2011; Tenaillon, 2014; McDonough & Connallon, 2023; McDonough, Ruzicka & Connallon, 2024). Moreover, the very conditions that lead to mutation-limited evolution also lead to heterozygote advantage among the mutations that facilitate the adaptive walk toward the optimum (see Fig. 6B). Heterozygote advantage among beneficial mutations can arise because heterozygotes approach the fitness optimum but homozygotes overshoot it (Sellis *et al.*, 2011), or because homozygotes express pleiotropic costs that are relatively well masked in heterozygotes (see Fig. 6A, where heterozygote advantage can occur for mutations increasing adaptation of trait 1 and pleiotropically reducing adaptation of trait 2). An adaptive walk of a diploid population is therefore characterised by a series of short-lived episodes of balancing selection in which individual beneficial alleles are subject to balancing selection immediately following their spread within the population, but these balanced polymorphic states are eventually perturbed by the spread of the next adaptive allele (Sellis *et al.*, 2011). These transient dynamics of balancing selection also emerge in trade-off scenarios, such as SA selection (Connallon & Clark, 2014), in which mutations exhibit net heterozygote advantage.

While transient episodes of balancing selection may occur during the evolutionary approach of a population to an optimum, conditions for long-term balancing selection become restrictive if there is sufficient genetic variation for the population to reach its optimum rapidly. In such cases, alleles whose homozygous carriers express the optimal phenotype will eventually become fixed (chapter 28 of Walsh & Lynch, 2018), and the ensuing stabilising selection on the trait will remove rather than preserve genetic variation. If no homozygous genotype corresponds to the optimum, a single long-term balanced polymorphism can be maintained, with the remaining loci experiencing purifying selection against whichever allele is rarest (Wright, 1935; Turelli & Barton, 2004). Still, opportunities for long-term balanced polymorphisms affecting a polygenic trait can expand if loci contributing to the trait are tightly linked (Gavrilets & Hastings, 1993; Bürger & Gimelfarb, 1999), if there is pervasive dominance reversal (Fig. 3) or 'diminishing-returns epistasis' (Wittmann *et al.*, 2017; Siljestam, Rueffler &

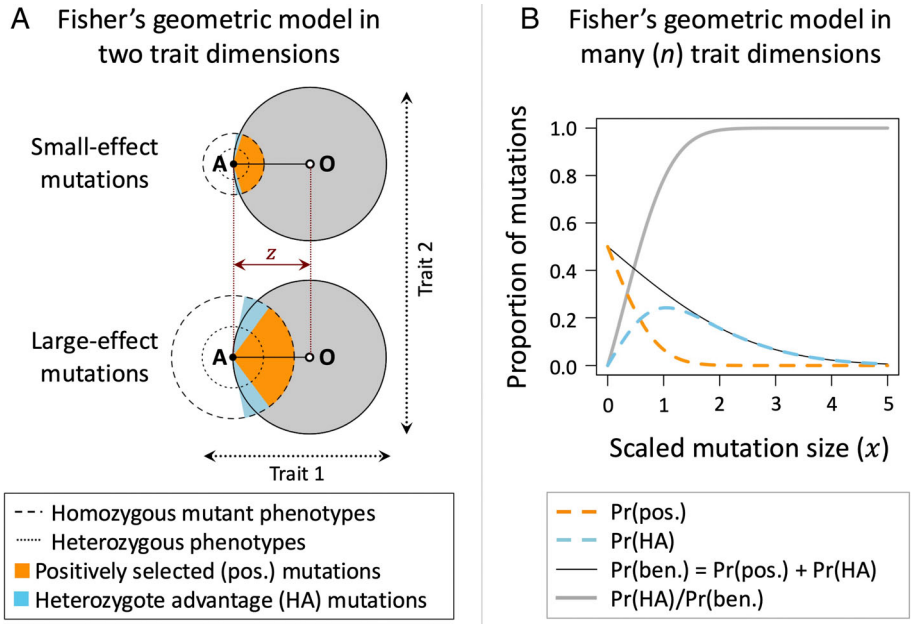

Fig. 6. Balancing selection in Fisher's geometric model. There are n traits selected to a single phenotypic optimum defined by the organism's environment, with **A** denoting the ancestral phenotype (homozygotes for the ancestral allele), **O** representing the optimum phenotype and z the distance to the optimum. Fitness declines with the distance between an individual's phenotype and the optimum, and mutations have random and unbiased orientations in n-dimensional phenotypic space. Pleiotropy, which is inherent in the model, can lead to trade-offs, in which mutations causing beneficial changes in some traits simultaneously cause harmful changes in others. (A) Illustration of a series of small-effect mutations (top) and large-effect mutations (bottom) for the case of $n = 2$ traits. Beneficial mutations (where heterozygous carriers are closer to the optimum than ancestral homozygotes) are comprised of positively selected mutations that are selectively favoured to fix (orange) and mutations exhibiting heterozygote advantage (blue) that are subject to balancing selection. (B) At high dimensions, the proportion of beneficial mutations that exhibits heterozygote advantage is predicted to increase with the scaled mutation size, $x = r\sqrt{n}/(2z)$, which depends on the number of traits (n), and the mutation's absolute phenotypic effect size (r) relative to the distance to the optimum (z). "Anisotropy" with respect to selection or mutational effects (i.e. variation among traits in the strength of stabilising selection, correlational selection, and non-random phenotypic effects of mutations) reduces the *effective* dimensionality of the system (Waxman & Welch, 2005; Martin & Lenormand, 2006; Svensson *et al.*, 2021).

Arnqvist, 2024), or if there is strong 'disruptive selection' favouring individuals at the trait extremes (Spichtig & Kawecki, 2004; Bürger & Gimelfarb, 2004), such as females and males (Flintham *et al.*, 2025).

Finally, while stabilising selection tends to remove polymorphism (with caveats noted above), polymorphism can still be maintained at a subset of loci affecting traits under stabilising selection, as long as such loci have pleiotropic effects on other fitness components. In models of 'pleiotropic balancing selection' (Robertson, 1956; Bulmer, 1973; Gillespie, 1984; Barton, 1990; Turelli & Barton, 2004), stabilising selection on the polygenic trait favours the removal of polymorphism at loci affecting the trait, whereas their effects on other fitness components favour balancing selection. Thus, one or more balanced polymorphisms can contribute to variation in a quantitative trait despite, rather than because of, stabilising selection on the trait. Both episodes of selection influence the overall evolutionary dynamics of each pleiotropic locus, and polymorphism is maintained if the variation-enhancing effects *via* other fitness components outweigh the variation-reducing effect of stabilising selection on the quantitative trait (for further discussion of pleiotropic balancing selection models and their quantitative predictions, see Appendix S4).

IV. LINKING THEORIES OF BALANCING SELECTION TO DATA

(1) The data

Before the genome era (Charlesworth, 2006), the catalogue of balanced polymorphisms was limited to a few textbook examples, such as the beta-globin gene which underlies sickle-cell anaemia in humans (Allison, 1954), *S*-loci which underlie self-incompatibility in plants (Emerson, 1938; Castric & Vekemans, 2004), the major histocompatibility complex which underlies immune diversity in vertebrates (Hedrick, 1998), and sex-determining genes which underlie even sex ratios (Fisher, 1930; Hasselmann & Beye, 2004). Since then, efforts to uncover the genetic basis of known trait polymorphisms have dramatically expanded the catalogue of

confirmed balanced polymorphisms (Llaurens *et al.*, 2017). To name a few: the *RXFP2* gene which affects horn size in the Soay sheep *Ovis aries* (Johnston *et al.*, 2013), the *BCMA1/3* locus which affects leaf chemical profiles in the rockcress *Boechera stricta* (Carley *et al.*, 2021), *R*-genes which confer parasite resistance in the thale cress *Arabidopsis thaliana* (Karasov *et al.*, 2014), a meiotic drive locus in the monkeyflower *Mimulus guttatus* (Fishman & Saunders, 2008), genes involved in synthesising galactose in the budding yeast *Saccharomyces cerevisiae* (Boocock *et al.*, 2021), *ABO* blood group genes in primates (Ségurel *et al.*, 2012), genes involved in venom production in *Crotalus* rattlesnakes (Schield *et al.*, 2022), cuticular hydrocarbon (*DsFAR2-B*), ethanol metabolism (*Aldh*) and anti-microbial resistance (*AMP*) genes in the fruit fly *Drosophila melanogaster* (Chakraborty & Fry, 2016; Unckless, Howick & Lazzaro, 2016; Rusuwa *et al.*, 2022), and a chromosomal inversion affecting a suite of life-history traits in the seaweed fly *Coelopa frigida* (Mérot *et al.*, 2020).

Balanced polymorphisms also contribute to striking behavioural phenotypes, such as the 'sitter' and 'rover' morphs of fruit fly larvae (Fitzpatrick *et al.*, 2007), foraging morphs in *Caenorhabditis elegans* (Greene *et al.*, 2016), three reproductive morphs in the ruff *Philomachus pugnax* (Lamichhaney *et al.*, 2016; Loveland *et al.*, 2025), the 'hunch' and 'flat' morphs of the dwarf spider *Oedothorax gibbosus* (Hendrickx *et al.*, 2021), and polygynous *versus* monogynous colonies of the fire ant *Solenopsis invicta* (Yan *et al.*, 2020). Finally, there is a plethora of colour polymorphisms with simple genetic bases, whose maintenance at intermediate frequencies strongly suggests balancing selection (Turelli & Barton, 2004). Such loci include the *P* and *H* loci of *Heliconius* and *Papilio* butterflies (Joron *et al.*, 2011; Kunte *et al.*, 2014), the *ZAL2* locus of the white-throated sparrow *Zonotrichia albicollis* (Tuttle *et al.*, 2016), the *tan* locus of *Drosophila erecta* (Yassin *et al.*, 2016), the *Red* locus of the Gouldian finch *Erythrura gouldiae* (Kim *et al.*, 2019), the *SPR* and *BCO2* loci of the common wall lizard *Podarcis muralis* (Andrade *et al.*, 2019), an indel in *Timema* stick insects (Villoutreix *et al.*, 2020), an inversion in *Ischnura* damselflies (Willink *et al.*, 2023) and two major SNPs in the kākāpō *Strigops habroptilus* (Urban *et al.*, 2024). In short, 'top-down' approaches are a fruitful way of identifying recent instances of balancing selection and describing their ecological context, painting rich portraits of the natural history of the balanced polymorphisms.

'Bottom-up' approaches, in which genomes are scanned for characteristic signatures of balancing selection, have also become a reliable source of evidence (reviewed in Fijarczyk & Babik, 2015; Bitarello *et al.*, 2023). Such approaches sidestep the substantial difficulties of measuring fitness in natural populations. They are also trait-agnostic, allowing detection of balancing selection candidates affecting any trait, including those that are difficult to measure with high levels of accuracy or replication. In this way, hundreds of candidate balanced polymorphisms have been identified, notably immunity-related loci in humans (Leffler *et al.*, 2013; DeGiorgio, Lohmueller & Nielsen, 2014; Siewert & Voight, 2017; Bitarello *et al.*, 2018; Giner-Delgado *et al.*, 2019; Aqil *et al.*, 2023), but also further loci in fruit flies (Croze *et al.*, 2017; Chapman, Hill & Unckless, 2019), plants (Wu *et al.*, 2017; Koenig *et al.*, 2019), crustaceans (Nunez *et al.*, 2021; Bourgeois *et al.*, 2021; Cornetti *et al.*, 2024; Murray *et al.*, 2025), and unicellular eukaryotes (Amambua-Ngwa *et al.*, 2012; Grace *et al.*, 2021). Although bottom-up approaches are best suited for identifying signals of long-term balancing selection, new methods are increasingly identifying recent signals as well (Isildak, Stella & Fumagalli, 2021; Soni, Vos & Eyre-Walker, 2022). Finally, evolve-and-resequence experiments can be used to uncover ongoing and/or recent balancing selection. Beyond classic studies of *Drosophila* inversion polymorphisms (Wright & Dobzhansky, 1946), recent efforts in *C. elegans* (Chelo & Teotónio, 2013), *D. melanogaster* (Kazancıoğlu & Arnqvist, 2014; Rostant *et al.*, 2015) and seaweed flies (Mérot *et al.*, 2020) have identified allele frequency signatures that are compatible with balancing selection.

(2) Contributions of balancing selection to molecular genetic variation

Despite ample empirical evidence for balanced polymorphisms, connecting these data with theoretical predictions remains challenging, as a citation network implies [Fig. 7, Appendix S5; see also Haller (2014) and Fitzpatrick *et al.* (2018)]. We do not know, for example, the fraction of genetic loci influenced by balancing selection. Is it closer to 0.1%, 1%, or 10%? Nonetheless, ongoing empirical research to estimate the important parameters of balancing selection models can guide our thinking on this question. For instance, the theory outlined in Section III.5 shows that transient balancing selection should be particularly common when evolution proceeds by adaptive walks involving large-effect mutations (recall that mutation 'size' is a function of pleiotropy and the distance of the population to the optimum; Fig. 6). Empirical work has indeed revealed many examples of large-effect loci contributing to adaptation of traits with small mutational targets (Bomblies & Peichel, 2022). Moreover, the genetic basis of polygenic traits sometimes includes a mixture of small- and large-effect loci, with the latter possibly maintained under balancing selection. This appears to be the case for cuticular hydrocarbon profiles in *Drosophila serrata* (Rusuwa *et al.*, 2022), age at maturity in the Atlantic salmon *Salmo salar* (Barson *et al.*, 2015), and horn size in Soay sheep (Johnston *et al.*, 2013). Common large-effect variants strongly suggest maintenance by balancing selection (Turelli & Barton, 2004), either due to direct selection on the trait of interest, or indirectly through pleiotropy and selection on another trait.

On the other hand, theory also shows that long-term stable balancing selection is unlikely when trait variation is highly polygenic (or multi-allelic), selection is stabilising, and pleiotropy is limited (see Section III.5). In such cases, a trait's genetic variation is predicted to be attributable to many rare alleles maintained at mutation–selection balance, with up to one locus under balancing selection (Wright, 1935; Turelli &

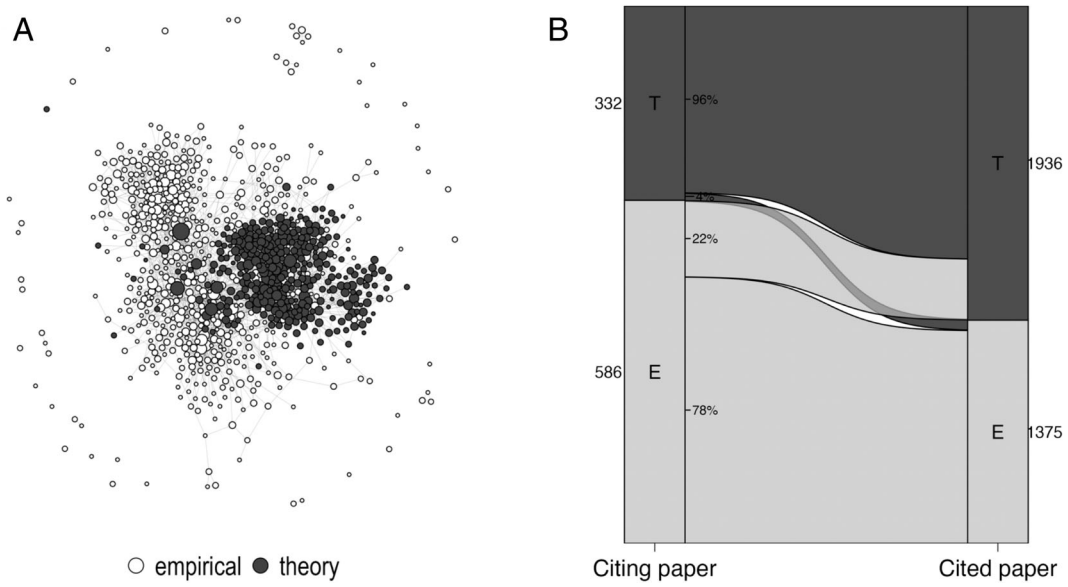

Fig. 7. Connections between balancing selection theory and data. (A) Citation network of theory and empirical papers. Each node (circle) represents one article in the dataset. Node colours denote article types (empirical, theory); node size is proportional to number of times the article is cited locally within the network (i.e. not the global citation count). (B) Citation patterns for each article type (E = empirical, T = theory) within the local network. Box and flow widths reflect the number of articles of a given type. See Appendix S5 for details of article collection methods. See Figs S3–S13 in Appendix S5 for further visualisations of the connections between theory and data, including timelines, citation networks, and journals in which papers were published.

Barton, 2004; Bürger & Gimelfarb, 2004). Such trait architectures are consistent with the observation that many traits are polygenic (Sella & Barton, 2019) and the absence of intermediate-frequency variants of large effect in genome-wide association studies (Abdellaoui *et al.*, 2023). Nevertheless, it is important to keep in mind that the populations and traits that have been targeted for intensive study are not necessarily representative traits, as each was chosen for personal, societal or logistical reasons. While it is certainly true that many well-studied traits are polygenic and continuously variable, others strongly deviate from the continuous polygenic ideal. In addition to visually conspicuous examples like colour patterns, traits associated with the basic molecular functions of individual genes (e.g. their binding, catalytic, and other cellular functions) have small mutational targets (e.g. genic mutation rates of order 10^{-6}) and are likely to display discontinuous patterns of genetic variability. Such 'molecular traits' are reasonable candidates for evolution by adaptive walks (Moutinho, Eyre-Walker & Dutheil, 2022), which *are* conducive to short-term episodes of balancing selection (Sellis *et al.*, 2011; Connallon & Clark, 2014). These adaptive-walk scenarios are unlikely to generate signals of long-term balancing selection (e.g. inflated linked heterozygosity, gene genealogies with long internal branches, or trans-species polymorphisms), but they can generate signals of short-term balancing selection [e.g. relatively low population genetic differentiation, or partial selective sweeps (Charlesworth, 2006; Sellis *et al.*, 2011; Soni *et al.*, 2022)]. Under this view, it is hardly surprising that some of our most compelling and well-understood examples of balancing selection are both short term and mediated by selection on fundamental protein structure and function.

Empirical research is also shedding light on other factors that affect the prevalence of balancing selection. For instance, interactions within and between loci (e.g. dominance reversals; diminishing-returns epistasis) can expand conditions for balancing selection (Arnqvist *et al.*, 2014; Wittmann *et al.*, 2017; Siljestam *et al.*, 2024). There is evidence for dominance reversals at major loci affecting life-history traits in Atlantic salmon, Soay sheep and *Drosophila* (Johnston *et al.*, 2013; Barson *et al.*, 2015; Karageorgi *et al.*, 2025) and in studies of quantitative traits, such as salinity tolerance in the copepod *Eurytemora affinis* (Posavi *et al.*, 2014) and fitness of the seed beetle *Callosobruchus maculatus* (Grieshop & Arnqvist, 2018), although it remains unclear whether such dominance reversals are common. Meanwhile, diminishing-returns epistasis for beneficial mutations appears to be common in microbial experiments (de Visser & Krug, 2014). Linkage between loci can also facilitate the establishment and maintenance of multi-locus balanced polymorphisms. Indeed, many of the best-characterised examples of balancing selection involve chromosome regions maintained as blocks of differentiated sequences (Llaurens *et al.*, 2017; Wellenreuther & Bernatchez, 2018). Finally, multi-locus balancing selection becomes likely when selection on traits is both strong and disruptive, rather than stabilising (Spichtig & Kawecki, 2004; Bürger & Gimelfarb, 2004; Flintham *et al.*, 2025). Analyses of large human data sets (Sanjak *et al.*, 2018) and *Drosophila* wing morphology (Houle *et al.*, 2017; Dugand *et al.*, 2021) suggest that stabilising

selection is more common than disruptive selection. However, estimates of non-linear (e.g. stabilising and disruptive) selection are notoriously noisy (Kingsolver *et al.*, 2001), and it remains unclear how often disruptive selection might play a role in generating balancing selection.

(3) Contributions of balancing selection to genetic variation for fitness and its components

One gets a clear sense from the literature that balancing selection probably occurs at few sites in a genome, and is therefore unlikely to explain most genome-wide molecular diversity. Yet the same is not necessarily true for the genetic variances of important phenotypes, life-history traits (i.e. fitness components like viability, longevity, and fertility) (Charlesworth & Hughes, 2000; Charlesworth, 2015; Sharp & Agrawal, 2018; Bonnet *et al.*, 2022), and overall fitness (Fowler *et al.*, 1997; Ruzicka *et al.*, 2019; Bonnet *et al.*, 2022; Singh, Hasan & Agrawal, 2023). Here, the contribution of balancing selection could be substantial because the genetic variance attributable to a single balanced polymorphism can be equivalent to many hundreds of loci evolving at mutation–selection balance (Crow, 1952, 1987; Charlesworth, 2015; Zajitschek & Connallon, 2018). As a result, balancing selection might account for a large proportion of the genetic variance of important phenotypes or fitness components, even if most loci within a genome are not subject to balancing selection. This potentially high contribution of balancing selection to genetic variances might explain why additive genetic variation (V_A) for major fitness components often exceeds predictions under mutation–selection balance alone (Charlesworth & Hughes, 2000; Charlesworth, 2015; Sharp & Agrawal, 2018).

Consider, for example, the case of a single locus with co-dominant, symmetric and antagonistic effects on two major fitness components (i.e. the AP model with parameters $s = s_1 = s_2$ and $h_1 = h_2 = 0.5$). At equilibrium, the contribution of the balanced polymorphism to the V_A of each fitness component will be $V_A = s^2/8$, whereas the variance contributed by a locus at mutation–selection balance will be $V_A \approx sh\mu$ (where μ is the mutation rate to the harmful allele, sh is its heterozygous fitness effect; the mutation is assumed to have equal negative effects on each fitness component; see Table 3). Given that mutation rates are typically orders of magnitude smaller than selection coefficients (Eyre-Walker & Keightley, 2007; Wang & Obbard, 2023), the contribution of each balanced polymorphism to V_A can be orders of magnitude greater than each locus at mutation–selection balance. Similar arguments apply to polygenic traits in which one locus is under balancing selection and the remaining trait-affecting loci are at mutation–selection balance (see Appendix S4).

In contrast to the predictions for individual phenotypes or fitness components, balancing selection is not necessarily expected to maintain V_A for overall fitness. At a stable polymorphic equilibrium, balancing selection is expected to contribute zero V_A for fitness under heterozygote advantage, negative frequency-dependent selection, and AP (Haldane, 1947; Charlesworth, 1987, 2015) (Table 3). However, there are important exceptions. For example, while heterozygote advantage generates zero V_A at equilibrium for an autosomal locus (Haldane, 1949), this is not true for an X-linked locus (Leach & Mayo, 1967). Balancing selection of SA alleles also contributes zero V_A for fitness at equilibrium if it is estimated in both sexes (e.g. through parent–offspring regression; Charlesworth, 1987), but V_A can be positive when estimated for each sex separately, e.g. through parent–offspring regression (Fedorka & Mousseau, 2004), hemi-clone designs (Chippindale, Gibson & Rice, 2001), or sex-specific genome-wide association studies (Ruzicka *et al.*, 2019). Similarly, balancing selection due to niche antagonism can generate V_A for fitness when it is estimated from individuals of the same niche (Charlesworth, 1987).

Finally, factors that prevent populations from reaching a stable equilibrium will cause balancing selection to contribute to V_A for fitness. Genetic drift, by causing random

Table 3. Genetic variances due to deleterious and balanced polymorphisms. Expressions for additive (V_A) and dominance (V_D) genetic variance are here compared under different population genetic models for the maintenance of genetic variation, including models of deleterious variation maintained at mutation–selection balance and various models of balancing selection (e.g. due to heterozygote advantage, the negative frequency-dependent selection model of Table 1, and a special case of antagonistic pleiotropy (AP) with co-dominant effects of alleles on a pair of fitness components). Here, μ is the mutation rate per gamete, s the homozygous fitness cost to carriers of the mutation, h is its dominance coefficient (approximations for mutation–selection balance assume that selection is strong relative to mutation: $sh \gg \mu$), and $\widehat{p}$ and $\widehat{q}$ are equilibrium allele frequencies for A_1 and A_2 alleles, respectively. Note that the contribution of deleterious alleles to the genetic variance of fitness components is expected to be lower than their contributions to overall fitness if there is positive pleiotropy between fitness components [i.e. if mutations typically have negative effects on multiple fitness components (Charlesworth, 2015; Maklakov, Rowe & Friberg, 2015)]. For example, a locus at mutation–selection balance that equally affects a pair of fitness components (i.e. the mutation has a heterozygous effect of $sh/2$ per fitness component), will contribute $V_A \approx sh\mu$ to each fitness component.

Selection scenario	V_A	V_D
Mutation–selection balance	$\sim 2sh\mu$	$\sim \frac{\mu^2}{h^2}(1-2h)^2$
Heterozygote advantage	0	$(\widehat{pq})^2(s_1+s_2)^2$
Negative frequency-dependent selection	0	0
Antagonistic pleiotropy		
Fitness component 1	$\widehat{pq}s_1^2/2$	0
Fitness component 2	$\widehat{pq}s_2^2/2$	0
Overall fitness	0	$(s_1 s_2 \widehat{pq}/2)^2$

displacements of the population from its polymorphic equilibrium, should generate some V_A for fitness under balancing selection. The combined effect of drift and balancing selection on V_A for fitness could be substantial in relatively small populations; intriguingly, high estimates of V_A for fitness have been found in well-monitored animal species with small population sizes (Bonnet *et al.*, 2022). In addition to drift, temporal fluctuations in the selection parameters that define balancing selection prevent populations from reaching equilibrium, leading to persistent V_A for fitness (Eshel & Hamilton, 1984; Charlesworth, 1987). The recent evidence from *Drosophila* populations that many intermediate-frequency alleles show rapid and predictable seasonal shifts in their frequencies (Bergland *et al.*, 2014; Machado *et al.*, 2021; Rudman *et al.*, 2022) is consistent with temporally fluctuating balancing selection maintaining substantial V_A for fitness.

V. CONCLUSIONS

(1) Balancing selection occurs when genetic polymorphism is maintained by selection in the absence of other processes such as migration, mutation or genetic drift. Under balancing selection, polymorphism is said to be 'protected' because both 'boundary equilibria' of a locus (i.e. $p=0$ and $p=1$) are unstable.

(2) The rate of publication of theory papers on balancing selection has ebbed and flowed since the 1920s. In the 1970s, the desire to account for the unexpected abundance of protein polymorphisms in nature marked a heyday for theoretical work on balancing selection. Genetic and genomic evidence for balancing selection has inspired a revival in recent years.

(3) Several scenarios can give rise to balancing selection: heterozygote advantage, negative frequency-dependent selection, and various trade-offs between contexts of selection. Many of these scenarios exhibit similar allele frequency dynamics. None of these scenarios necessarily lead to balancing selection and conditions leading to loss of polymorphism are often more permissive than conditions leading to maintenance of polymorphism, depending on the details of the model (e.g. strength of selection, dominance, transmission advantage).

(4) Over the last century, theoreticians have gradually explored deviations from idealised models in which a single locus evolves in a large, diploid, randomly mating population. For example, inbreeding, haploidy and haplo-diploidy often depress the scope for balancing selection, while linkage between loci often expands it. In finite populations, a locus subject to balancing selection can harbour more, or less, variation than a neutral locus, depending on the strength of balancing selection and the polymorphism's deterministic equilibrium.

(5) To predict the prevalence of balancing selection, we need models that incorporate a genotype–phenotype map. In models where traits evolve by 'adaptive walks' to an optimum, short-lived episodes of balancing selection emerge readily. In models where trait variation is highly polygenic, selection is stabilising, and pleiotropy is limited, opportunities for balancing selection become restrictive.

(6) The connections between data and theory on balancing selection remain very loose. For example, we do not know what proportion of genetic polymorphism is maintained – directly or indirectly – by balancing selection. But even if the proportion of polymorphic loci affected by balancing selection is small, the proportion of genetic variation for fitness (and fitness components) accounted for by balancing selection may still be large because balanced polymorphisms make disproportionate contributions to the variance of traits and fitness components, compared with deleterious mutations. There remains a pressing need to quantify the relative contributions of different scenarios of balancing selection and recurrent mutation to different components of fitness variance.

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VIII. SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. The basics.
Appendix S2. Balancing selection in haploids and haplodiploids.
Appendix S3. Balancing selection in finite populations.
Appendix S4. Effects of balanced polymorphisms on the expression of traits selected toward an optimum.
Appendix S5. Publication patterns in balancing selection research.
Data S1. Bibtex file containing full bibliography of theoretical papers on balancing selection.
Data S2. RDS file containing full bibliography of empirical papers on balancing selection.

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