1 Different mechanisms drive the maintenance of
2 polymorphism at loci subject to strong versus
3 weak fluctuating selection

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Abstract

20 The long-running debate about the role of selection in maintaining ge-
 21 netic variation has been given new impetus by the discovery of hundreds
 22 of seasonally oscillating polymorphisms in wild *Drosophila*, possibly stabi-
 23 lized by an alternating summer-winter selection regime. Historically there
 24 has been skepticism about the potential of temporal variation to balance
 25 polymorphism, because selection must be strong to have a meaningful
 26 stabilizing effect — unless dominance also varies over time (“reversal of
 27 dominance”). Here we develop a simplified model of seasonally variable
 28 selection that simultaneously incorporates four different stabilizing mech-
 29 anisms, including two genetic mechanisms (“cumulative overdominance”
 30 and reversal of dominance), as well as ecological “storage” (“protection
 31 from selection” and boom-bust demography). We use our model to com-
 32 pare the stabilizing effects of these mechanisms. Although reversal of
 33 dominance has by far the greatest stabilizing effect, we argue that the
 34 three other mechanisms could also stabilize polymorphism under plausi-
 35 ble conditions, particularly when all three are present. With many loci
 36 subject to diminishing returns epistasis, reversal of dominance stabilizes
 37 many alleles of small effect. This makes the combination of the other
 38 three mechanisms, which are incapable of stabilizing small effect alleles,
 39 a better candidate for stabilizing the detectable frequency oscillations of
 40 large effect alleles. (199 words)

41 Keywords: balancing selection, rapid adaptation, polygenic adaptation, eco-
 42 evolutionary dynamics

1 Introduction

Understanding how populations maintain genetic variation for fitness-associated traits is a foundational problem in evolutionary biology. In the “classical view”, genetic variation appears by mutation and is removed by a combination of selection and random genetic drift, resulting in unstable variation that continually turns over. In contrast, the “balance view” posits that genetic variation is stably maintained by selection.

The theoretical basis of mutational variation is simple: mutations will maintain variation if mutation rates are sufficiently high. Empirically, deleterious mutation rates can sometimes exceed one per individual per generation (Lynch et al., 1999; Lesecque et al., 2012), and it is well established that transient mutations contribute substantially to standing genetic variation in fitness-associated traits (Keightley and Halligan, 2008; Charlesworth, 2015).

The contribution of balancing selection to standing genetic variation can also be substantial (Bitarello et al., 2018; Good et al., 2017; Charlesworth, 2015). In a particularly striking example, sequencing studies in temperate *Drosophila* populations have found hundreds of polymorphic loci which undergo seasonal oscillations in allele frequency (Bergland et al., 2014; Machado et al., 2018). Many of these polymorphisms appear to be ancient (Bergland et al., 2014), suggesting pervasive, long-term balancing selection.

The possibility of pervasive balancing selection poses a theoretical problem. Unlike the case of mutational variation, the conditions leading to balanced polymorphism are not resolved (Yi and Dean, 2013; Svardal et al., 2015; Wittmann et al., 2017). Fundamentally, stable polymorphism requires negatively frequency-dependent selection, i.e. low frequency alleles must be favored over high frequency alleles. In temporally and spatially uniform environments, instances of negative frequency-dependence are largely restricted to immune system genes (Aguilar et al., 2004), Batesian mimicry (Kunte, 2009) and self-

71 incompatibility loci (Charlesworth, 2006). Heterogeneous selection substantially
72 broadens the types of loci potentially subject to negative frequency-dependence,
73 since the latter only needs to arise when averaged over the environmental het-
74 erogeneity, rather than within each generation, or within spatially homogeneous
75 subpopulations (Frank and Slatkin, 1990; Svardal et al., 2015). The theoretical
76 problem is to explain how environmental heterogeneity can lead to sufficiently
77 strong balancing selection under a plausible range of conditions.

78 In the *Drosophila* example above, polymorphism appears to be stabilized by
79 temporal heterogeneity, specifically adaptation to alternating seasonal selection
80 regimes (Bergland et al., 2014; Machado et al., 2018). Inspired by this example,
81 we restrict our attention to temporal heterogeneity (for discussion of spatial
82 heterogeneity see Frank and Slatkin (1990); Hedrick (2006); Svardal et al. (2015)
83 and references therein). We distinguish between two broad classes of mechanism
84 by which temporal heterogeneity can stabilize polymorphism.

85 The first are mechanisms which rely on purely genetic factors such as diploid
86 Mendelian inheritance and epistasis. Early studies of fluctuating selection fo-
87 cused on the consequences of incomplete dominance. Rare alleles all appear in
88 heterozygotes, and so incomplete dominance can reduce selection against rare
89 alleles in the environments they are unsuited to, making selection negatively
90 frequency-dependent (Dempster, 1955; Haldane and Jayakar, 1963). Following
91 Dempster (1955), we call this “cumulative overdominance”.

92 “Reversal of dominance” (also known as “segregation lift”; Wittmann et al.
93 2017) also relies on diploid Mendelian inheritance, but additionally requires
94 dominance to change over time such that the favored allele at any moment is
95 dominant. Reversal of dominance was the basis of Gillespie’s SAS-CFF model
96 of non-neutral genetic variation (Gillespie, 1978; Hedrick, 1986). More recently,
97 Wittmann et al. (2017) showed that reversal of dominance can simultaneously
98 stabilize hundreds of polymorphic loci in mutation-selection balance, without
99 an attendant genetic load problem (i.e. the large number of segregating loci

100 did not imply fitness differences so large that they require an implausibly large
101 reproductive capacity; see also Gillespie 2010, pp. 74).

102 Sign epistasis between locus pairs can stabilize polymorphism via an in-
103 teraction with linkage disequilibrium (Novak and Barton, 2017). While this
104 mechanism may be important at some loci, we will not discuss it further be-
105 cause it is not clear how it should be applied to more than two loci (other than
106 that there are simply many pairs of sign-epistatic loci).

107 Our second class of stabilizing mechanisms are ecological i.e. they depend
108 on ecological interactions between individuals rather than genetic interactions
109 between alleles. We consider two mechanisms in particular, which are both par-
110 ticular instances of the “storage effect”. The storage effect encompasses a broad
111 class of fluctuation-dependent coexistence scenarios with potentially very differ-
112 ent biological underpinnings (Chesson, 2000). Historically, the storage effect
113 was introduced using a model with two life stages, adults and juveniles, with
114 overlapping generations and competition among juveniles only (Chesson and
115 Warner, 1981). In this model, some adults are “stored” over multiple rounds
116 of juvenile recruitment without themselves experiencing competition. This re-
117 duces losses in unfavorable environments, and allows rare genotypes to rapidly
118 recoup their losses when favorable environmental conditions return. Overlap-
119 ping generations and similar phenomena like resting eggs in *Daphnia* have so far
120 been the focus of genetic applications of the storage effect (Ellner and Hairston
121 1994; Yi and Dean 2013; Hedrick 2006; Svardal et al. 2015; although see Gulisija
122 et al. 2016 for an epistatic interpretation of the storage effect). What ties these
123 phenomena together is “protection from selection”, that is, a fraction of each
124 genotype/species experiences weakened selection. This is the first of our ecolog-
125 ical mechanisms.

126 The storage effect also includes scenarios where there is no protection from
127 selection in the above sense. We will consider a stabilization phenomenon that
128 occurs when population density undergoes repeated “boom-bust” demographic

cycles (Yi and Dean, 2013; Li and Chesson, 2016), as is the case in temperate *Drosophila* populations driven in part by seasonal variation in fruit availability (Bergland et al., 2014). This phenomenon is a consequence of crowding effects at higher densities, which can result in longer generation times. When a rapid summer grower genotype is common, the population will reach high densities more rapidly than when a slow-growing winter-adapted type is common, resulting in fewer versus more generations of selection in the summer for the two respective cases. This creates frequency-dependent selection for the seasonal cycle as a whole, which can stabilize polymorphism (Yi and Dean, 2013).

The preceding paragraphs demonstrate that there is no shortage of mechanisms that can stabilize polymorphism in the presence of temporal variability. Nevertheless, temporal variability has not been regarded as a robust basis for arguing that balanced polymorphism should be prevalent, or for explaining known balanced polymorphisms, even though temporal variability is ubiquitous. The reason for this is that most stability mechanisms based on temporal variability require fluctuating selection to be strong in order to have an appreciable stabilizing effect (Hoekstra et al., 1985; Smith and Hoekstra, 1980; Hedrick, 1986, 2006). That is, selection must strongly favor different genotypes at different times to be able to counteract a non-negligible difference in time-averaged genotypic fitness. For example, taken in isolation, cumulative overdominance is too weak to stabilize polymorphism unless selection coefficients are at least of order 0.1 (Hoekstra et al., 1985, Fig. 3). By comparison, in the above *Drosophila* example the overall absolute change in allele frequency over a season — which constitutes multiple generations — is itself only of order ~ 0.1 , implying smaller selection coefficients (Wittmann et al., 2017; Machado et al., 2018).

Reversal of dominance is the major exception to the strong-selection requirement, and has recently been investigated as a possible candidate to explain multi-locus balancing selection in *Drosophila* (Wittmann et al., 2017). However, escaping the strong selection requirement means that reversal of dominance can

158 stabilize alleles of weak effect, which poses different problems. Under the empir-
 159 ically well-supported assumption of diminishing-returns epistasis (Chou et al.,
 160 2011; Kryazhimskiy et al., 2014), Wittmann et al. (2017) found that the ma-
 161 jority of polymorphic loci in mutation-selection-drift balance had fitness effects
 162 so small that their frequency oscillations were undetectable — at most ~ 10
 163 detectably oscillating loci could be stabilized. Because reversal of dominance
 164 is able to stabilize polymorphism between segregating alleles with weak fitness
 165 effects, the model predicted the accumulation of weak-effect polymorphic loci.
 166 In the presence of diminishing returns epistasis, this accumulation made the
 167 model incapable of generating stable polymorphisms of sufficiently strong ef-
 168 fects to match the many detectably oscillating loci that have been observed
 169 in *Drosophila*. We are therefore faced with the conundrum that most of the
 170 stability mechanisms dependent on temporal variability require selection that
 171 is implausibly strong, but the more effective reversal of dominance mechanism
 172 allows selection to be so weak as to create other difficulties (it is also unknown
 173 whether reversal of dominance is likely to be prevalent in nature; see Gillespie
 174 1978 and Wittmann et al. 2017 for discussion).

175 Here we argue that ecological coexistence mechanisms help to explain how it
 176 is possible to have a large number of detectably oscillating polymorphisms stabi-
 177 lized by temporal variability. The ecological mechanisms we consider also have
 178 a strong selection requirement, offering nothing new over and above cumulative
 179 overdominance in this respect. However, we will show that the ecological mecha-
 180 nisms operate in conjunction with cumulative overdominance. This expands the
 181 region of allelic fitness effects compatible with balanced polymorphism, partly
 182 mitigating the strong selection requirement. Moreover, this mitigation occurs
 183 in such a way that the diminishing returns problem that arises with reversal
 184 of dominance (discussed above) is avoided. Together these results give a more
 185 favorable view of the stabilizing potential of temporal variability, and could help
 186 to explain the *Drosophila* findings of Bergland et al. (2014) and Machado et al.

187 (2018).

188 Our analysis rests on a simplified model of fluctuating selection that in-
189 corporates reversal of dominance, cumulative overdominance, protection from
190 selection, and boom-bust demography all at once. We assume that the environ-
191 ment alternates between two states, “summer” and “winter”. This significantly
192 simplifies the mathematical analysis compared to the more general case of a
193 stochastic environment (e.g. Chesson and Warner 1981). We use our model to
194 derive a combined stability condition including the effects of all of these mech-
195 anisms, which reveals both their individual contributions to stability, as well as
196 their interactions.

197 2 Basic model and assumptions

198 Our basic model is a straightforward extension of the standard equations for
199 selection in diploids. We assume that a winter allele W and a summer allele S
200 are segregating at one locus in a randomly mating population. Each iteration
201 of the model involves one round of random mating and juvenile recruitment to
202 reproductive maturity. Some fraction of the copies of each allele are completely
203 “protected” from selection, so that the allele frequencies within the protected
204 fraction remain constant from one iteration to the next. The classic example of
205 this form of protection is generational overlap (Chesson and Warner, 1981): if
206 only a fraction $1 - f$ of reproductively mature individuals die and are replaced
207 each round of juvenile recruitment, then alleles in the remaining fraction f
208 experience no viability selection. Note that the particular copies of each allele
209 that are protected may change between iterations. The environment alternates
210 between summer and winter such that the per-iteration relative fitnesses of
211 unprotected alleles take the values in Table 1. The change in winter allele
212 frequency p_W over one iteration is thus given by

$$p'_W = [f + (1 - f) \frac{w_{WW}p_W + w_{SW}p_S}{\bar{w}}]p_W, \quad (1)$$

	Summer homozygote	Heterozygote	Winter homozygote
Summer	$w_{SS}(S) = 1 + a_S$	$w_{SW}(S) = 1 + d_S a_S$	$w_{WW}(S) = 1$
Winter	$w_{SS}(W) = 1$	$w_{SW}(W) = 1 + d_W a_W$	$w_{WW}(W) = 1 + a_W$

Table 1: Relative fitness values for unprotected summer/winter alleles in an alternating summer/winter environment. The variables a_S and a_W denote the juvenile advantages of the S and W alleles in the summer and winter respectively.

and similarly for the summer allele, where $\bar{w} = p_S^2 w_{SS} + 2p_S p_W w_{SW} + p_W^2 w_{WW}$ is the mean relative fitness of unprotected alleles. If there is no protection ($f = 0$), we have the usual $p'_W = \frac{w_{WW} p_W + w_{SW} p_S}{\bar{w}} p_W$.

For polymorphism between W and S to be stable, both W and S alleles must increase in frequency over a full summer/winter cycle when rare. We will generally assume that the winter allele is rare ($p_W \ll 1$); the behavior of a rare summer allele will then be obtained by swapping the S and W labels. Since W is rare, p_W^2 terms are negligibly small in Eq. (1), which thus simplifies to

$$p'_W = [f + (1 - f) \frac{w_{SW}}{w_{SS}}] p_W. \quad (2)$$

Eq. (2) expresses the fact that almost all individuals are S homozygotes, and almost all copies of W occur in heterozygotes.

We denote number of summer and winter iterations by i_S and i_W respectively. Therefore, the condition for the rare winter allele to increase in frequency over a complete seasonal cycle is

$$\left[f + (1 - f) \frac{w_{SW}(S)}{w_{SS}(S)} \right]^{i_S} \left[f + (1 - f) \frac{w_{SW}(W)}{w_{SS}(W)} \right]^{i_W} > 1. \quad (3)$$

Eq. (3) will be the foundation for much of the analysis presented below. When we come to consider boom-bust population demography we will also evaluate some extensions of Eq. (3) that are better equipped for handling the effects of non-constant population density.

3 Results

3.1 Stabilizing mechanisms

In this section we compare four mechanisms that can stabilize polymorphism at a single locus in the presence of fluctuating selection: cumulative overdominance, reversal of dominance, protection from selection, and boom-bust population demography. We start by considering the first three of these separately, since these are substantially simpler to analyze in the absence of boom-bust demography. In particular, we can make the simplifying assumption that i_S and i_W are constants (that is, in each season selection proceeds in the same way for a fixed number of iterations; as we will see, this is not the case in the presence of boom-bust demography).

To further simplify, we begin by setting $i_S = i_W$ (unequal but constant values of i_S and i_W do not induce frequency-dependence and thus do not stabilize polymorphism). It is then straightforward to show that Eq. (3) becomes (details in Appendix A)

$$(1 - d_S)a_S - d_W a_W < [f + (1 - f)d_S]d_W a_S a_W. \quad (4)$$

Below we use special cases of Eq. (4) to isolate the effects of cumulative overdominance, reversal of dominance, and protection from selection. We then extend our analysis to incorporate the effects of boom-bust population demography.

3.1.1 Cumulative overdominance and reversal of dominance

We first consider the case of no protection ($f = 0$) in Eq. (4). Polymorphism can then be stabilized in two distinct ways. First, cumulative overdominance (Dempster, 1955) is a consequence of weakened negative selection on rare winter alleles in the summer due to incomplete dominance. Its effect can be seen most easily by assuming that dominance is constant between seasons, such that the winter dominance is the complement of the summer dominance $d_W = 1 - d_S$.

Eq. (4) then simplifies to

$$a_S - a_W < d_S a_S a_W. \quad (5)$$

Eq. (5) shows that the rare winter allele can persist even if the summer allele is superior ($a_S > a_W$). The stabilizing effect gets stronger with increasing summer dominance d_S . Strong fluctuating selection is needed for stability, since the product of juvenile advantages $a_W a_S$ appears on the right hand side (the asymmetry between allelic fitness effects can be at most second order in the juvenile advantages a_S and a_W).

Combining Eq. (5) with the corresponding condition for a rare summer allele (given by Eq. (5) with the S and W labels swapped) defines a region of stable polymorphism for a given dominance (Fig. 1a, red). The requirement for strong fluctuating selection can be seen not just by the small size of the red region as a whole, but more specifically by the way it tapers to little more than a line for small values of a_S and a_W .

The second way that stable polymorphism can occur is reversal of dominance. This requires dominance to alternate between seasons. For simplicity, let the magnitude of alternating dominance be constant, i.e. $d_S = d_W = d$. Then Eq. (4) can be written as

$$\frac{1-d}{d} a_S - a_W < d a_S a_W. \quad (6)$$

The right hand side of Eq. (6) represents the effects of cumulative overdominance (compare Eq. (5)). The effects of reversal of dominance can be viewed in isolation by setting this term to zero,

$$\frac{1-d}{d} a_S - a_W < 0. \quad (7)$$

In Eq. (7), the summer advantage a_S is multiplied by the factor $(1-d)/d$, which is smaller than 1 if the favored allele is dominant ($d > \frac{1}{2}$). This stabilizes polymorphism by partly offsetting any advantage that the common summer allele

Figure 1: (a) Cumulative overdominance alone only stabilizes a small region (red; $d_S = d_W = 0.5$ in Eq. (5)), especially if selection does not fluctuate strongly (a_S and a_W are not large). Reversal of dominance creates a much larger region of stability (blue; $d = 0.6$ in Eq. (7)). (b) Protection from selection in haploids (Eq. (8)) stabilizes a region with the same shape as cumulative overdominance in diploids, and magnitude set by f . In diploids with both cumulative overdominance and protection from selection, the stabilized region is only modestly larger than protection from selection in haploids (blue; $d_S = d_W = 0.5$ and $f = 0.5$ in Eq. (4)). (c) Boom-bust demography alone (red; $c = 0.5$ in Eq. (11)) is similar to cumulative overdominance, but is not symmetric (more of the red lies below than above the dashed line) since it hinges on the summer advantage a_S . (d) Reversal of dominance alone (blue; Eq. (7)) is effective at stabilizing alleles of any strength, but the combination of cumulative overdominance and protection from selection (red) is similarly effective for larger effect alleles.

may have. Unlike cumulative overdominance, which is second order in the juvenile advantages, reversal of dominance has a first order effect (Fig. 1a, blue). This powerful effect arises because rare alleles are more often found in heterozygotes, thus granting them the major benefit that heterozygotes are always closer in fitness to the favored homozygote than to the unfavored homozygote.

3.1.2 Protection from selection

We now examine the effects of protection from selection, allowing $f > 0$ (but still keeping the number of summer and winter iterations equal $i_S = i_W$). We do this in two stages for ease of comparison with the diploid case discussed above. First, we consider a haploid variant of our model where the winter genotype has $w_W(S) = 1$ and $w_W(W) = 1 + a_W$, and the summer genotype $w_S(S) = 1 + a_S$ and $w_S(W) = 1$. It is then easily verified that the condition for persistence of a rare winter allele is

$$a_S - a_W < f a_S a_W \quad (8)$$

This condition can be derived from scratch in a similar way to Eq. (4). Alternatively, we can simply observe that the haploid case is a special instance of the diploid model where $d_S = 0$ and $d_W = 1$ when the winter allele is rare, and $d_S = 1$ and $d_W = 0$ when the summer allele is rare (compare the haploid fitnesses with Table 1, and then substitute these values into Eq. (4)).

Eq. (8) is the same condition as Eq. (5), but with d_S replaced by f . Thus, as in the case of cumulative overdominance, stable polymorphism under protection from selection requires fluctuating selection to be strong (Fig. 1b, red). Intuitively, protection favors rarity because, in the absence of protection, an abundant type can easily displace a large fraction of a rare type's individuals when the abundant type is favored, due to sheer numerical advantage. Protection thus limits the rare type's fractional losses. By contrast, a rare type can only displace a tiny fraction of an abundant type's individuals when the

304 rare type is favored, and its growth is therefore not limited by protection of the
305 abundant type.

306 In diploids, the effect of protection from selection is represented by the $f +$
307 $(1 - f)d_S$ factor on the right hand side of Eq. (4), representing an increase
308 of $(1 - f)d_S$ over the corresponding factor in the haploid case Eq. (8). This
309 increase gets smaller for larger f , because cumulative overdominance only affects
310 unprotected allele copies.

311 3.1.3 Boom-bust demography

312 We now derive a condition analogous to Eq. (4) that accounts for an additional
313 source of negative frequency dependence induced by boom-bust demography.
314 This boom-bust demography stabilizing mechanism requires: (1) alternating
315 periods of population expansion and collapse; (2) selection favoring the S allele
316 in the summer must be weaker at higher population density; (3) the overall
317 amount of growth in the summer (as measured by the growth factor D from
318 summer start to summer end) must be frequency-independent. We comment on
319 the plausibility of (2) and (3) at the end of this section; first we illustrate the
320 essential features of the boom-bust demography stabilizing mechanism by con-
321 sidering an idealized scenario in which selection ceases entirely at high density
322 (our approach follows Yi and Dean (2013)).

323 Although our basic model Eq. (1) does not explicitly represent population
324 density, it can nevertheless be used to illustrate the boom-bust stabilizing mech-
325 anism by relaxing our previous assumption that i_S is constant. To show why
326 this is so, we first assume for simplicity that there is no protection (the in-
327 teraction between protection and boom-bust demography is addressed in the
328 following section). Next, we assume that each genotype grows at a constant
329 rate in the summer (r -selection). These genotype-specific absolute growth rates
330 are assumed to be proportional to the relative fitnesses in Table 1, and will
331 be denoted by r . For instance, the abundance of a rare winter allele grows

332 according to $n'_W = r_{SW}(S)n_W$, while $n'_S = r_{SS}(S)n_S$ for the summer allele,
 333 where $r_{SW}(S) = (1 + d_S a_S)r_{WW}(S)$ and $r_{SS}(S) = (1 + a_S)r_{WW}(S)$. Density-
 334 dependence is incorporated by assuming that total population density N reaches
 335 carrying capacity before the end of summer, at which point selection ceases en-
 336 tirely (satisfying condition (2)).

337 The winter is assumed to consist of density-independent mortality at a con-
 338 stant rate α such that, in the rare- W case, $n'_W = \alpha \frac{w_{SW}(W)}{w(W)}n_W$ and $n'_S =$
 339 $\alpha \frac{w_{SS}(W)}{w(W)}n_S$ where $\alpha < 1$ and w is defined in Table 1. Ecologically, this could
 340 represent the gradual loss of viable overwintering sites, with the winter allele
 341 being better at securing and holding those sites. Since the population growth
 342 factor D in the summer is equal to the winter decline when the boom-bust cycle
 343 is in a steady state, this winter mortality model ensures that D is frequency-
 344 independent such that it has the same value in the rare- S and rare- W cases.

345 The allele frequencies in the above model obey Eq. (1) with $f = 0$, and
 346 so Eq. (3) applies with $f = 0$. However, the number of iterations of selection
 347 in the summer i_S is not constant in Eq. (3), as was assumed in the preceding
 348 sections. Now i_S depends on how many iterations of growth it takes for the pop-
 349 ulation to reach carrying capacity. This induces negative frequency-dependence
 350 because the common type determines the mean population growth rate. Thus,
 351 a lower winter allele frequency implies more rapid population saturation, and
 352 hence fewer iterations of negative selection experienced by the winter allele.
 353 Conversely, a lower summer allele frequency implies more iterations of positive
 354 selection on the summer allele (Fig. 2). The result is a stabilizing effect.

355 In Appendix B we use Eq. (3) to quantify the boom-bust stabilizing effect
 356 under the above assumptions. The number of summer iterations i_S is shown to
 357 depend on frequency as follows

$$i_{S|S_{\text{rare}}} \approx i_W(1 + ca_S) \quad i_{S|W_{\text{rare}}} \approx i_W(1 - ca_S), \quad (9)$$

358 where c is a constant approximately equal to $1/2$. The difference in i_S between

the summer-rare versus winter-rare frequency regimes is therefore first order in the summer advantage a_S . This introduces second order terms into the stability condition Eq. (4), giving

$$(1 - d_S)a_S - d_W a_W < d_S d_W a_S a_W + c(1 - d_S)a_S^2. \quad (10)$$

The condition for a rare summer allele to grow is obtained as before by swapping labels in all terms apart from the last, which is replaced by $cd_S a_S^2$ (details in Appendix B). Similar to our analysis of protection from selection, the effect of boom-bust demography can be isolated by considering the haploid case ($d_S = 0$ and $d_W = 1$ when the winter allele is rare, $d_S = 1$ and $d_W = 0$ when the summer allele is rare), which gives

$$a_S - a_W < ca_S^2 \quad (11)$$

for a rare winter allele (and $a_W - a_S < ca_S^2$ for rare S).

Eq. (10) and (11) show that the strength of the boom-bust stabilizing mechanism is second order in the juvenile advantages, like cumulative overdominance and protection from selection, but with the difference that the stabilizing term depends on the summer advantage only (Fig. 1c, red). Eq. (10) also shows that there is no interaction between the stabilizing contributions of boom-bust demography and cumulative overdominance (the corresponding terms on the right hand side are simply added). Intuitively we do not expect dominance to affect the boom-bust mechanism because the latter depends on the growth rate of W and S homozygotes; these determine the overall population growth rate when the corresponding allele is common.

The above model of constant growth followed by stasis at carrying capacity follows Yi and Dean’s (2013) model of coexistence in a microbial serial transfer experiment. The alternating “seasons” in Yi and Dean (2013) are both booms, each followed by a selectively neutral dilution step by a fixed dilution factor D . Here the environmental cycle only involves a single boom followed by a non-neutral bust, and we have shown that a rarity advantage can also arise in this

Figure 2: Illustration of a winter/summer boom-bust demographic cycle in a simplified model of exponential growth up to saturation in the summer, and exponential decline in the winter. The periods of selection in the summer and winter are marked with green and blue boxes respectively. Selection ceases when total population density is at carrying capacity, causing there to be more iterations of summer selection when the summer allele is rare.

385 case under conditions (1)-(3).

386 Are conditions (2) and (3) plausible? The density-dependent selection in (2)
387 could reflect trade-offs between traits favorable at low vs high densities, but (2)
388 could also occur simply because less selection occurs at high density compared
389 to the initial low-density “boom” (e.g. due to reduced population turnover).
390 Condition (3) is open to the objection that we might expect total population
391 size at the end of the winter to be smaller if the winter survivor W is rare
392 than if it is common (Fig. 2). In this case the summer growth factor D up
393 to carrying capacity would itself depend on frequency in a way that eliminates
394 the rarity advantage induced by density-dependent growth (there would be no
395 negative frequency dependence if we had assumed r -selection in the winter as
396 well). Thus, the plausibility of condition (3) hinges on the extent to which
397 selection in the winter represents simple differences in extrinsic mortality rates
398 versus a relatively inflexible population bottleneck (e.g. scarce overwintering
399 sites).

400 To complete our analysis of the boom-bust stabilizing mechanism, we supple-
401 ment the above proof of principle with a simulation example that incorporates a
402 more realistic description of density-dependence. To preclude the possible stabi-
403 lizing effects of diploidy discussed in the preceding sections, we restrict ourselves
404 to the haploid case. We assume that growth in the summer follows the Ricker
405 model $n'_S = e^{r_S(1-N/K)}n_S$ and $n'_W = e^{r_W(1-N/K)}n_W$ where $r_S = (1 + a_S)r_W$
406 and $N = n_S + n_W$. This model ensures that selection favoring the S allele
407 gets weaker at higher densities (condition (2) above). Our motivation for us-
408 ing the Ricker model is that the comparably simple discrete-time logistic model
409 $n'_S = r_S(1 - N/K)n_S$ does not satisfy condition (2) because selection is density-
410 independent (unless we additionally assume that K differs between alleles; this
411 is both more complicated and potentially introduces coexistence in a constant
412 environment which would make analysing the boom-bust stabilizing mechanism
413 impossible). Winter mortality is the haploid version of the model used above to

414 obtain Eq. (10). Fig. 3 shows the frequency and abundance trajectories of S and
 415 W haplotypes coexisting stably due to the boom-bust demography coexistence
 416 mechanism.

Figure 3: An example of haploid polymorphism stabilized by boom-bust demography where selection in the summer follows the Ricker model $n'_S = e^{r_S(1-N/K)}n_S$ and winter mortality occurs at a constant rate $n'_S = b_S n_S$ (blue areas indicate the summer allele). Parameters: $\alpha = 0.6$, $a_W = 0.1$, $r_S = 0.7$, $a_S = 0.2$, $K = 10^5$, 10 generations/season.

417 3.1.4 Combining protection and boom-bust demography

418 In the previous section we gave a simplified treatment of the boom-bust sta-
 419 bilizing mechanism, which assumed (among other things) that there was no
 420 protection. Here we consider the combined effects of protection and boom-bust
 421 demography.

422 In addition to allowing the boom-bust stabilizing mechanism to occur, boom-
 423 bust demographic cycles can also modify the stabilizing effects of protection,
 424 even if the boom-bust stabilizing mechanism is not present (e.g. because selec-
 425 tion favoring the summer allele in the summer does not get weaker with in-
 426 creasing density). The reason is that the effect of protecting a fraction f of the
 427 allele copies in a given iteration depends on how many juveniles are recruited in
 428 the next iteration. There will be essentially no protective effect if the protected
 429 alleles are swamped by juveniles during a demographic boom, and conversely
 430 the protective effect is amplified in a shrinking population. To illustrate this
 431 point, consider a simple extension of Eq. (2) which allows population density to
 432 vary depending on the magnitude of juvenile recruitment:

$$n'_W = [f + \alpha(1 - f)\frac{w_{SW}}{w_{SS}}]n_W, \quad (12)$$

433 and similarly for a rare summer allele. Here α represents the magnitude of
 434 juvenile recruitment, and takes the constant values $\alpha_S > 1$ in the summer and
 435 $\alpha_W < 1$ in the winter (our original model Eq. (2) is retrieved when $\alpha_S =$
 436 $\alpha_W = 1$, corresponding to constant total population size N). If the population
 437 is expanding rapidly ($\alpha_S \gg 1$), then the f term in Eq. (12) will be negligibly
 438 small by comparison and it will be as though there is no protection in the
 439 summer. Conversely, the influence of the f term will be amplified in the winter
 440 (when $\alpha_W < 1$) compared to Eq. (2).

441 To measure the stabilizing effect in Eq. (12), we calculate the average of each
 442 allele's growth when rare over a full seasonal cycle,

$$\frac{1}{2} \left(\left. \frac{p_{\text{initial}} - p_{\text{final}}}{p_{\text{initial}}} \right|_{S_{\text{rare}}} + \left. \frac{p_{\text{initial}} - p_{\text{final}}}{p_{\text{initial}}} \right|_{W_{\text{rare}}} \right), \quad (13)$$

443 where the juvenile advantages $a_S = a_W$ are assumed to be equal. Eq. (13)
 444 allows us to quantify stabilizing effects numerically when we do not have neat
 445 analytical results such as Eq. (4). Importantly, since we average over the two
 446 rarity cases, Eq. (13) is not sensitive to any asymmetries between winter and

447 summer that might intrinsically favor the S or W allele even though $a_S = a_W$.
 448 Such asymmetries could be confused for a rarity advantage/disadvantage if only
 449 one of the rarity scenarios is examined in isolation, and are difficult to avoid in
 450 all but the simplest models (e.g. Eq. (2)). The stabilizing effect of protection
 451 in Eq. (12), as measured by Eq. (13), can be enhanced or diminished relative
 452 to the constant- N case depending on the values of α_S , α_W and f . The effect is
 453 enhanced in many cases of biological relevance; Fig. 4 shows two examples (solid
 454 and black dashed lines). Intuitively, the reason for this is that the enhanced
 455 protective effect due to the winter bust $\alpha_W < 1$ expands the overall region of
 456 coexistence more than the reduced protective effect due to the summer boom
 457 truncates the region of coexistence — but the region of coexistence will be
 458 asymmetric (see Appendix C for more details).

459 Having considered the effects of boom-bust cycles on protection, we now
 460 turn to the interaction between the boom-bust stabilizing mechanism and pro-
 461 tection. Intuitively, we expect that the combination of protection from selec-
 462 tion and boom-bust demography will be “zero-sum” because these mechanisms
 463 are most effective under contrasting conditions. Protection is most effective in
 464 crowded conditions; protection only inhibits the growth of a common allele if
 465 it must displace the rare allele to grow (see “Protection from selection”). On
 466 the other hand, the boom-bust stabilizing mechanism is most effective when
 467 summer growth starts in uncrowded conditions, since this allows for the largest
 468 proportional weakening in the strength of selection due to density-dependence
 469 (see “Boom-bust demography”).

470 Eq. (12) thus exaggerates the stabilizing potential of protection, because
 471 juvenile recruitment is modeled as though conditions are crowded at all popu-
 472 lation densities (the juvenile recruitment rate is divided by the mean relative
 473 fitness). To represent the fact that selection at low densities will typically occur
 474 in uncrowded conditions, we consider a slightly modified version of Eq. (12) in

the summer

$$n'_W = [f + \alpha_S(1 - f) \left(1 - \frac{N}{K}\right) w_{SW}] n_W, \quad (14)$$

and similarly for a rare summer allele. Here $N = n_S + n_W$, and K represents the environmental carrying capacity. In Eq. (14), selection favoring the summer allele gets weaker as density increases (provided that $f \neq 0$), as required for the boom-bust stabilizing mechanism to work. At low population densities there is no competition and selection is based purely on intrinsic growth rates (r -selection). On the other hand, once the population has grown to high density and reached equilibrium, N must be constant which implies that the population mean absolute fitness $f + \alpha_S(1 - f) \left(1 - \frac{N}{K}\right) \bar{w}$ is equal to 1. Substituting this equilibrium requirement into Eq. (14) brings us back to our basic model Eq. (2) again, where selection happens in crowded conditions.

In Fig. 4 we compare the rarity advantages obtained from simulations of Eq. (12) and Eq. (14). It can be seen that, in both of these models, boom-bust demography has a stabilizing effect. The stabilizing effects of protection in Eq. (12) (solid black line) are indeed exaggerated compared to the more realistic treatment of density dependence in Eq. (14) (red line). Nevertheless, the rarity advantage in the latter resulting from the combination of protection in a variable population, cumulative overdominance, and the boom-bust stabilizing mechanism, is still substantially stronger than protection and cumulative overdominance in a constant population (blue line; i.e. the situation summarized by Eq. (4)).

3.2 Stabilizing weak versus large effect alleles

In sections 3.1.1-3.1.3 we showed that, for polymorphism to be stable, the difference between a_S and a_W (which represents the extent to which one allele is superior to the other over a seasonal cycle), can be at most first order in the juvenile advantages under reversal of dominance, but at most second order

Figure 4: The mere presence of boom-bust cycles enhances the stabilizing effect of protection (solid and dashed black lines; Eq. (12)) compared to the case where N remains constant (blue line), even in the absence of the boom-bust stabilizing mechanism. The red line shows the rarity advantage in Eq. (14), which captures the combined effects of protection, cumulative overdominance, and the boom-bust stabilizing mechanism (this is our more realistic model, in which crowding gradually becomes more important with increasing density and selection is density-dependent). The quantity on the vertical axis is defined in Eq. (13). Simulation parameters: $f = 0.5$, $\alpha_W = 0.5$, $d_S = d_W = 0.5$, $i_S = i_W = 10$, $N_{\text{initial}} = 10^3$, $K = 10^5$.

under the other three mechanisms. This has consequences for the stabilization of alleles with weak versus strong fitness effects.

The “effectiveness” of stabilization can be quantified in terms of the greatest difference in juvenile advantages a_S and a_W compatible with stable polymorphism. The simple difference $a_S - a_W$ is not a good measure of effectiveness because the magnitude of this difference will often be proportional to the magnitude of the underlying advantages (the contribution of a locus to fitness sets the scale for a_S and a_W , as well as their difference). Thus, the fact that the regions of stability in Fig. 1 grow wider for larger a_S and a_W does not mean that stabilization is more effective, because the allelic differences that would typically need to be stabilized are growing as well. Consequently, a better measure of effectiveness is the greatest proportional difference compatible with stable polymorphism, given by $\frac{a_S - a_W}{a_W}$ for a rare winter allele, and $\frac{a_W - a_S}{a_S}$ for a rare summer allele.

In the case of reversal of dominance, a rare winter allele can stably segregate with a summer allele with advantage up to $a_S = \frac{d}{1-d}a_W$, and so the effectiveness of balancing selection is a constant $\frac{d}{1-d} - 1$. Thus, reversal of dominance is equally effective at stabilizing alleles with weak or strong fitness effects. This results in a broad region of stability even for small juvenile advantages (Fig. 1d).

On the other hand, the effectiveness of balancing selection for cumulative overdominance in Eq. (5) is $d_S a_S$ (or $d_W a_W$ for a rare summer allele). Thus, balancing selection is completely ineffective for alleles with very small juvenile advantages, but becomes more effective as the juvenile advantages increase. Similar results apply for protection from selection and boom-bust demography. The combined stability region for cumulative overdominance, protection from selection and boom-bust demography is thus negligibly small for small a_S and a_W (Fig. 1d, red), but rapidly becomes comparable to the reversal of dominance stability region as the juvenile advantages increase. The combination of cumulative overdominance, protection from selection, and boom-bust demogra-

phy therefore filters out alleles with weak effect while stabilizing stronger effect alleles.

3.3 Juvenile advantages and the strength of selection

Cumulative overdominance, protection from selection, and boom-bust demography require $a_S, a_W \sim 0.1$ or more to have a meaningful “effectiveness” (see preceding section). Eq. (4) implies an effectiveness of $\approx 10\%$ when the juvenile advantages are ≈ 0.1 . The permissible difference $a_W - a_S$ grows rapidly with increasing a_S thereafter. Such values may seem implausibly high to be prevalent in nature. Even in the temperate *Drosophila* case, where selection at the individual level is regarded as strong, the total change in allele frequencies over a season is only of order ~ 0.1 . The number of generations per season is not known (Machado et al., 2018), but each season probably constitutes multiple generations (e.g. Wittmann et al. (2017) suggest ~ 10 generations/season). At face value this does not seem compatible with selection strong enough to allow cumulative overdominance, protection from selection, and boom-bust demography to be effective.

In Fig. 5, we compute the juvenile advantage implied by a given seasonal allele frequency change for an allele at intermediate frequencies. For simplicity, we assume that only protection from selection and cumulative overdominance are present. Since we are considering alleles at intermediate frequencies we use Eq. (1)). Following the temperate *Drosophila* case, we set our given allele frequency change as an increase of 0.1 over the summer from $p_S = 0.45$ to $p_S = 0.55$ (most of the fluctuating loci observed by Machado et al. (2018) exhibited smaller fluctuations of $0.04 - 0.08$ per season but it is not clear which of these are balanced versus hitchhiking; we follow (Wittmann et al., 2017) in using 0.1 as a representative figure). We consider a range of possible values of summer iterations $i_S = 10 - 20$. This range of values is based on the assumption

that each “season” constitutes half a year, and that the portion of the life cycle from egg laying to reproductive maturity takes $\sim 10 - 15$ days in *Drosophila* (corresponding to one iteration of our model). Fig. 5 shows that the summer advantage must be at least $a_S \sim 0.05$ for a seasonal allele frequency change of 0.1. Larger values are needed if there is protection, or if fewer iterations occur per season.

4 Discussion

We have analyzed four different mechanisms that induce balancing selection under temporal variation, the resulting effectiveness of balancing selection, and how these mechanisms interact. Previous analyses critiquing the stabilizing potential of temporal variability considered cumulative overdominance and reversal of dominance only (Smith and Hoekstra, 1980; Hoekstra et al., 1985; Hedrick, 1986), and concluded that only reversal of dominance has a strong enough stabilizing effect to be taken seriously as a basis for balanced polymorphism. Here we also consider the ecological effects of protection from selection and boom-bust demography. In our model, the juvenile advantages a_S and a_W determine whether selection is strong enough for balanced polymorphism (Fig. 1). Protection from selection and boom-bust demography expand the region of juvenile advantages compatible with stable polymorphism. Moreover, we show that seasonal allele frequency changes of ~ 0.1 , as observed in temperate *Drosophila* populations, imply juvenile advantages of at least ~ 0.05 , with larger values needed in the presence of protection (Fig. 5). Together these findings suggest that the scope for temporal variability to balance polymorphism is wider than previous analyses appreciated (Smith and Hoekstra, 1980; Hoekstra et al., 1985; Hedrick, 1986), particularly due to mechanisms other than reversal of dominance.

Figure 5: (a) Juvenile advantages of at least ~ 0.05 per iteration are needed to produce a total juvenile allele frequency change of 0.1. Larger values are needed in the presence of protection, or if there are fewer rounds of juvenile recruitment each season. The change in allele frequency is given by Eq. (1). (b) An example of stable polymorphism assuming protection from selection and cumulative overdominance only ($i_S = 10$, $a_S = 0.2$, $a_W = 0.21$, $f = 0.5$, $d_S = d_W = 0.5$ in Eq. (4)). After running for 100 seasonal cycles to ensure that the steady-state cycle has been reached, the summer allele oscillates between $p = 0.3$ and $p = 0.4$.

583 4.1 Empirical tests and implications

584 Protection from selection and cumulative overdominance

585 The protection from selection mechanism is probably widespread, given some
586 amount of protection from the overlapping generations of iteroparous organisms.
587 However, protection from selection will not be effective at stabilizing polymor-
588 phism unless selection is also strong, as measured by the juvenile advantages
589 a_S and a_W . Similar considerations apply for cumulative overdominance; the
590 required incomplete dominance is also likely to be widespread, but will not be
591 effective at stabilizing polymorphism unless selection is strong. The strong se-
592 lection requirement presumably limits the prevalence of these mechanisms as a
593 stabilizers of polymorphism. However, as we have seen in Sec. 3.3, *Drosophila*
594 data are compatible with juvenile advantages being surprisingly large, partic-
595 ularly if the fraction of protected alleles f is appreciable. Specifically, Fig. 5
596 suggests that juvenile advantages of order ~ 0.1 are compatible with the magni-
597 tude of allele frequency oscillations; this is strong enough for mechanisms other
598 than reversal of dominance to stabilize polymorphism.

599 Estimating the magnitude of f is challenging. In many models with pro-
600 tection, generational overlap is the primary form of protection, fecundity re-
601 mains constant with age, and total population density is constant (Chesson and
602 Warner, 1981; Ellner and Hairston, 1994; Svardal et al., 2015). The strength
603 of protection f is then simply the fraction of surviving adults each round of
604 juvenile recruitment. With this simple model in mind we can get a rough
605 estimate of the magnitude of f in wild *Drosophila* from laboratory measure-
606 ments. Female fecundity peaks ≈ 5 days after reaching reproductive maturity
607 but egg laying continues up to 20 days after which female survivorship declines
608 rapidly (Le Bourg and Moreau, 2014). We approximate this as death occurring
609 at 20 days. Assuming that it takes 10 days to develop from an egg to reproduc-
610 tive maturity, this means that females persist for roughly two rounds of juvenile

611 recruitment under laboratory conditions. This corresponds to a protection due
612 to overlapping generations of $f = 0.5$. This number is probably an overestimate
613 since females in the wild are subject to additional sources of mortality such as
614 predation and parasitism, and female fecundity declines with age.

615 In reality, protection is more complicated. Adults may also experience some
616 selection, e.g. due to predation/parasites. In this case, protected alleles only
617 experience weakened negative selection, not complete protection; $f + (1 - f) \frac{w}{w}$
618 in Eq. (2) would then be replaced by $f \frac{w_P}{w_P} + (1 - f) \frac{w_U}{w_U}$ where P and U stand for
619 “protected” and “unprotected”, respectively. Additional complications arise in
620 an expanding population. For instance, the strength of protection may depend
621 on how rapidly the population is growing; even if the proportion of surviving
622 adults is large, they will only constitute a small fraction of the population if a
623 large number of juveniles is recruited to adulthood each iteration. Other forms of
624 protection include maternal effects, which can confer protection because, in any
625 given iteration, some fraction of unfavored alleles will have a favored mother (e.g.
626 the heterozygote offspring of a summer homozygote in the summer). We would
627 then need to distinguish between the possible parental combinations that an
628 allele might experience (Wolf and Wade, 2016). The development of population
629 genetic methods to quantify protection from selection is needed.

630 Finally, note that protection depends upon the presence of crowding (sec-
631 tion “Combining protection and boom-bust demography”). While crowding is
632 likely to be important in organisms with relatively stable demography, which
633 are presumably at or near their environmental carrying capacity, the presence
634 of strong crowding effects is less certain in populations which undergo cyclical
635 collapses in population density.

636 **Boom-bust demography**

637 Boom-bust demography is distinguished by its reliance on density-dependent se-
638 lection induced by crowding. A relatively simple way to test for the presence of

639 stabilization driven by boom-bust demography would be to alleviate the effects
 640 of crowding by artificially constraining density e.g. via culling of adults. Adult
 641 culling would also mitigate the effects of overlapping generations (which would
 642 also be affected by changes to crowding). If boom-bust demography is indeed
 643 stabilizing polymorphism, we would then expect temporally-averaged allele fre-
 644 quencies to shift (potentially even losing the polymorphism), as a result of the
 645 weakening of the boom-bust demography rarity advantage.

646 **Reversal of dominance**

647 Reversal of dominance is distinguished by its high effectiveness: it is an order of
 648 magnitude stronger than cumulative overdominance, protection from selection
 649 and boom-bust demography. Among the mechanisms considered here, reversal
 650 of dominance is unique in being insensitive to the magnitude of the juvenile ad-
 651 vantages (Sec. 3.2). Thus, we might be able to test for the presence of reversal
 652 of dominance stabilization by experimentally weakening the juvenile advantages
 653 a_S and a_W by similar proportions. We would then expect to only see a reduc-
 654 tion in the amplitude of allele frequency oscillations, with comparatively little
 655 change in temporally-averaged allele frequencies. The reason for this is that the
 656 temporally-averaged allele frequency is set by a balance between the superior
 657 juvenile advantage of one allele and the rarity advantage of the other; under re-
 658 versal of dominance these both scale with the juvenile advantage. By contrast,
 659 under cumulative overdominance, protection from selection and boom-bust de-
 660 mography, the rarity advantage rapidly disappears for smaller a_S and a_W , and
 661 we would expect to see the allelic superiority overwhelming it if we weaken
 662 selection.

663 **Multi-locus polymorphism**

664 Our analysis has considered the simple case of two alleles segregating at a sin-
 665 gle locus. To understand pervasive balancing selection we must confront the

multi-locus case (Wittmann et al., 2017), which requires us to account for the interactions between loci. These interactions can occur via linkage or epistasis. Note that, even if recombination rates are high, overlapping generations in the presence of selection will generate linkage disequilibrium. Linkage can either act to preserve or eliminate genetic variation at a given locus depending on whether nearby loci are under directional or balancing selection. As such, linkage does not directly promote or eliminate balanced polymorphism (although linkage can stabilize polymorphism in combination with sign epistasis; Novak and Barton 2017).

Many different forms of epistasis are possible, some of which can dramatically alter the stability of polymorphism at individual loci (Novak and Barton, 2017; Gulisija et al., 2016). However, at the genomic scale there is empirical support for diminishing returns epistasis when combining the beneficial effects of segregating alleles across loci (Chou et al., 2011; Kryazhimskiy et al., 2014). Diminishing returns epistasis has important consequences for multi-locus polymorphism if weak effect alleles can be stabilized: weak effect polymorphic loci will accumulate and preclude larger effect polymorphisms from being present in mutation-selection-drift balance as a result of diminishing returns (Wittmann et al., 2017). This poses a problem for reversal of dominance, but not cumulative overdominance, protection from selection and boom-bust demography (Sec. 3.2).

We can therefore make the following conclusions about multi-locus polymorphism in *Drosophila*. If reversal of dominance is indeed responsible for balancing these polymorphisms, then it must somehow get around its weak allele problem. One way this might occur is if reversing dominance is less likely to occur in weak effect alleles. Unless there is a solution to the weak allele problem, mechanisms which do not stabilize weak effect alleles must be responsible for stabilizing many of the observed polymorphisms (assuming that these alleles are indeed balanced; migration is one important alternative); this could include

the three weaker mechanisms considered here. Although we have shown that seasonally oscillating selection in *Drosophila* could plausibly be strong enough for these weaker mechanisms to be effective, a more definitive conclusion rests upon either estimating the magnitude of f , or on direct measurements of the juvenile advantages a_S and a_W .

4.2 Extensions and limitations

Much of our analysis rests on standard population genetic models of selection in diploids, and is therefore subject to the usual caveats (e.g. the lack of frequency-dependence in a_S and a_W , nonrandom mating, and so on). Our extension of these standard models to incorporate protection is derived from classical models of protection induced by generational overlap (Chesson and Warner, 1981; Svardal et al., 2015). As discussed above, our description of protection would need to be modified to describe more complicated forms of protection.

In our treatment of boom-bust demography we have only considered one model that explicitly represents density-dependent selection (Eq. (14)). Many other choices are possible here, which could depend on the model of protection. The variable-density territorial contest model of Bertram and Masel (2019), which has overlapping generations as its protection mechanism, is one possibility for exploring some of these issues. One important possibility that we have not discussed is if density dependence causes selection to switch sign such that the winter type is favored at high density (e.g. due to a growth/competitive ability trade-off). We have specifically avoided this scenario here since it would allow polymorphism in a stable environment and our focus is on fluctuation-dependent stability mechanisms.

Due to our focus on fluctuation-dependent stability mechanisms, we have also not attempted to explore spatial variation or phenotypic variation within genotypes (individual variation), or how different sources of variation interact

722 (see Frank and Slatkin (1990) and Svardal et al. (2015)).

723 When evaluating whether two alleles will stably persist, we have taken the
724 allelic juvenile advantages to be fixed quantities. In the long term the juvenile
725 advantages will evolve, leaving open the possibility that polymorphism is not
726 evolutionarily stable (Ellner and Hairston, 1994). This scenario is addressed
727 by Svardal et al. (2015), who derive conditions for polymorphism in variable
728 environments based on “evolutionary branching”. That is, Svardal et al. (2015)
729 require a rarity advantage at an attractor in the dynamics of a quantitative trait
730 evolving by sequential substitutions of small effect mutations. Our model does
731 not have any attractors in this sense, because in the absence of further assump-
732 tions, evolution will favor generalist alleles with ever increasing advantages in
733 both seasons. This is not biologically reasonable because it fails to account for
734 trade-offs in traits associated with summer versus winter success. In the absence
735 of a model of these trade-offs, it is therefore not possible to further connect the
736 findings of Svardal et al. (2015) to ours.

737 This points to a broader divide between population genetic and more pheno-
738 typic approaches (such as adaptive dynamics) to the study of genetic variation.
739 Adaptive dynamics approaches typically view variation through the lens of evo-
740 lutionary branching, which implies disruptive selection at the phenotypic level.
741 One consequence of disruptive selection is that fitness-associated genetic varia-
742 tion is expected to become concentrated at a few loci, not dispersed over many,
743 because recombination is more likely to produce less fit intermediate phenotypes
744 when genetic variation is dispersed (Kopp and Hermisson, 2006; van Doorn and
745 Dieckmann, 2006; Svardal et al., 2015). The population genetic approach does
746 not require phenotypic disruptive selection, and predicts no tendency for genetic
747 variation to be concentrated (Wittmann et al., 2017). However, population ge-
748 netic approaches generally do not specify the phenotypic basis of selection at all.
749 This quickly becomes problematic when trying to account for ecological factors,
750 as we have seen in the case of boom-bust demography. There is therefore a need

751 to better integrate the population genetic and phenotypic approaches.

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871 **Appendix A: Details of the diploidy and protec-** 872 **tion from selection conditions**

873 Here derive the condition for stable polymorphism under the combined effects
874 of diploid Mendelian inheritance and protection from selection, Eq. (8). Recall
875 that this condition assumes $i_S = i_W$, and so we can take the i_W 'th root to
876 remove the exponents in Eq. (3). Multiplying by $w_{SS}(S)w_{SS}(W)$, Eq. (3) can
877 thus be written as

$$[fw_{SS}(S) + (1-f)w_{SW}(S)][fw_{SS}(W) + (1-f)w_{SW}(W)] > w_{SS}(S)w_{SS}(W). \quad (15)$$

878 Substituting from Table 1 we have,

$$[f(1+a_S) + (1-f)(1+d_Sa_S)][f + (1-f)(1+d_Wa_W)] > 1 + a_S, \quad (16)$$

879 which can be simplified to

$$[1 + (f + (1-f)d_S)a_S][1 + (1-f)d_Wa_W] > 1 + a_S. \quad (17)$$

880 Multiplying out the square brackets and subtracting the right hand side gives

$$(f-1)a_S + (1-f)d_Sa_S + (1-f)d_Wa_W + (1-f)(f + (1-f)d_S)a_Sd_Wa_W > 0. \quad (18)$$

881 Dividing by $(1-f)$ then gives

$$(d_S - 1)a_S + d_Wa_W + (f + (1-f)d_S)a_Sd_Wa_W > 0, \quad (19)$$

882 which yields Eq. (4).

883 **Appendix B: Details of the boom-bust condition**

884 Here we derive Eq. (10), which gives gives the condition for stable polymorphism
885 in the presence of boom-bust population demography assuming a simplified rep-
886 resentation of density-dependence in which only r -selection occurs (see section
887 “Boom-bust demography” for assumptions and notation).

888 If the winter allele is rare, the summer homozygote determines the overall
889 rate of population expansion, and we have $(b_{SS})^{i_{S|W_{\text{rare}}}} = D$, or equivalently
890 $i_{S|W_{\text{rare}}} = \ln D / \ln b_{SS}$. On the other hand, if the summer allele is rare, then
891 $i_{S|S_{\text{rare}}} = \ln D / \ln b_{WW} = \ln D / [\ln b_{SS} - \ln(b_{SS}/b_{WW})]$, where $b_{SS}/b_{WW} =$
892 $w_{SS}(S)/w_{WW}(S) = 1 + a_S$. Thus, to first order in a_S we have $\ln b_{SS}/b_{WW} \approx a_S$,
893 and

$$\begin{aligned} i_{S|S_{\text{rare}}} &\approx \frac{\ln D}{\ln b_{SS} - a_S} \\ &= \frac{\ln D}{\ln b_{SS}} \frac{1}{1 - a_S / \ln b_{SS}} \\ &\approx i_{S|W_{\text{rare}}} (1 + a_S / \ln b_{SS}). \end{aligned} \quad (20)$$

894 Defining $i = (i_{S|S_{\text{rare}}} + i_{S|W_{\text{rare}}})/2$ as the “baseline” number of summer itera-
895 tions, we therefore have $i_{S|S_{\text{rare}}} \approx i(1 + ca_S)$ and $i_{S|W_{\text{rare}}} \approx i(1 - ca_S)$ to first
896 order in a_S , where $c = 1/(2 \ln b_{SS})$.

897 The strength of the boom-bust stabilizing mechanism is controlled by the
898 constant $c = 1/(2 \ln b_{SS})$. This dependence of c on b_{SS} is a consequence of
899 the discrete-time nature of our model. In the continuous time limit where
900 each iteration represents a vanishingly small growth increment, $c \rightarrow 1/2$ and
901 the boom-bust stability mechanism depends entirely on relative ratios between
902 absolute Malthusian parameters (compare Yi and Dean 2013). In practice, c
903 will typically be of close to $1/2$ unless growth is extremely rapid (e.g. $c \approx 0.72$ in
904 a population which doubles every summer iteration). We therefore set $c = 1/2$
905 in Fig. 1.

906 For simplicity, in Eq. (9) we assume symmetry between the seasons, such
907 that the winter has the same number of iterations as the baseline number of
908 summer iterations, i.e. $i_W = i$ with $i_S = i_W$ in the case where $a_S = 0$. In the
909 asymmetric case where either summer or winter is intrinsically longer, a different
910 region of juvenile advantages can permit stable polymorphism. For instance, the
911 summer advantage must be larger for a given winter advantage if $i_W > i$. But

912 this asymmetry does not affect the overall magnitude of the stabilized region,
 913 because constant differences between i_S and i_W do not introduce frequency
 914 dependence.

915 Taking the i_W 'th root of Eq. (3) with $f = 0$, our stability condition for a
 916 rare winter allele can thus be written analogously to Eq. (17) as

$$[1 + d_S a_S]^{i_S/i_W} [1 + d_W a_W] > (1 + a_S)^{i_S/i_W}, \quad (21)$$

917 where $i_S/i_W = 1 - ca_S$. We then apply the generalized binomial theorem: $(1 +$
 918 $x)^r = 1 + rx + \frac{r-1}{2!}x^2 + \dots$. This implies $(1 + a_S)^{1-ca_S} = 1 + (1 - ca_S)a_S + O(a_S^3)$,
 919 and similarly $[1 + (f + (1 - f)d_S)a_S]^{1-ca_S} = 1 + (f + (1 - f)d_S)(1 - ca_S)a_S +$
 920 $O(a_S^3)$. Neglecting third order terms in a_S , Eq. (21) is thus the same as Eq. (17),
 921 but with a_S replaced by $(1 - ca_S)a_S$ and $f = 0$. The same steps used to obtain
 922 Eq. (4) from Eq. (17) (Appendix A) will therefore yield Eq. (4) with a_S replaced
 923 by $(1 - ca_S)a_S$. In the resulting inequality, the ca_S contribution on the right
 924 hand side is $O(a_S^3)$ and can be neglected, and we move the ca_S contribution on
 925 the left hand side to the right to obtain Eq. (10).

926 The corresponding condition for a rare summer allele is obtained by swapping
 927 S and W labels in Eq. (17) and then replacing $a_S \rightarrow (1 - ca_S)a_S$, again neglecting
 928 $O(a_S^3)$ terms and setting $f = 0$. The ca_S contribution on the left now appears
 929 in the term $-d_S(1 - ca_S)a_S$; the boom-bust demography term on the right is
 930 thus $cd_S a_S^2$ for a rare summer allele.

931 **Appendix C: Protection in the presence of boom-** 932 **bust cycles**

933 Here we give some mathematical details of how protection behaves in the pres-
 934 ence of boom-bust cycles. Applying the same procedure as outlined in Appendix
 935 A to the haploid version of Eq. (12), it can be shown that the condition for stable

936 polymorphism is given by

$$\begin{aligned}
 a_W - a_S + f\left(\frac{\alpha_W - 1}{\alpha_W}a_S - \frac{\alpha_S - 1}{\alpha_S}a_W\right) &< \frac{f}{\alpha_W}a_Sa_W \\
 a_S - a_W + f\left(\frac{\alpha_S - 1}{\alpha_S}a_W - \frac{\alpha_W - 1}{\alpha_W}a_S\right) &< \frac{f}{\alpha_S}a_Sa_W
 \end{aligned} \tag{22}$$

937 for the rare- S and rare- W cases respectively. The last term on the left represents
 938 the fact that the juvenile advantages a_S and a_W no longer contribute on equal
 939 terms to per-capita growth due to the asymmetrical effects of protection in the
 940 summer and winter. This term simply switches sign when the S and W labels
 941 are switched in the rare- W versus rare- S cases, and it therefore makes zero
 942 contribution to the overall advantage of rarity in Eq. (13). The enhancement
 943 of the overall region of stability arises due to the fact that in a population
 944 undergoing boom-bust cycles, $1/\alpha_W \gg 1$ on the right hand side. Provided that
 945 the boom-bust cycles are large enough (i.e. α_W is small enough), this will more
 946 than offset the loss of coexistence due to the fact that $1/\alpha_S < 1$ in the rare- W
 947 case — but the region of coexistence will now be asymmetric.