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

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Abstract

The long-running debate about the role of selection in maintaining genetic variation has been given new impetus by the discovery of hundreds of seasonally oscillating polymorphisms in wild *Drosophila*, possibly stabilized by an alternating summer-winter selection regime. Historically there has been skepticism about the potential of temporal variation to balance polymorphism, because selection must be strong to have a meaningful stabilizing effect unless dominance also varies over time ("reversal of dominance"). Here we develop a simplified model of seasonally variable selection that simultaneously incorporates four different stabilizing mechanisms, including two genetic mechanisms ("cumulative overdominance" and reversal of dominance), as well as ecological "storage" ("protection from selection") and boom-bust demography. We use our model to compare the stabilizing effects of these mechanisms. Although reversal of dominance has by far the greatest stabilizing effect, we argue that the three other mechanisms could also stabilize polymorphism under plausible conditions, particularly when all three are present. With many loci subject to diminishing returns epistasis, reversal of dominance stabilizes many alleles of small effect. This makes the combination of the other three mechanisms, which are incapable of stabilizing small effect alleles, a better candidate for stabilizing the detectable frequency oscillations of large effect alleles. (199 words)

Keywords: balancing selection, rapid adaptation, polygenic adaptation, eco-evo

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, 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-

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

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

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

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

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

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

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

The storage effect also includes scenarios where there is no protection from selection in the above sense. We will consider a stabilization phenomenon that 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. 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 stabilize alleles of weak effect, which poses different problems. Under the empir-

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

Here we argue that ecological coexistence mechanisms help to explain how it is possible to have a large number of detectably oscillating polymorphisms stabilized by temporal variability. The ecological mechanisms we consider also have a strong selection requirement, offering nothing new over and above cumulative overdominance in this respect. However, we will show that the ecological mechanisms operate in conjunction with cumulative overdominance. This expands the region of allelic fitness effects compatible with balanced polymorphism, allowing balanced polymorphism to occur for more modest fitness effects. Moreover, for alleles of small effect the expansion of the region of balanced polymorphism is negligible, such that small effect polymorphisms will not be stabilized, avoiding the difficulty that arises with reversal of dominance discussed above. Together these results give a more favorable view of the stabilizing potential of temporal variability, and could help to explain the *Drosophila* findings of Bergland et al.

(2014) and Machado et al. (2018).

Our analysis rests on a simplified model of fluctuating selection that incorporates reversal of dominance, cumulative overdominance, protection from selection, and boom-bust demography all at once. We assume that the environment alternates between two states, "summer" and "winter". This significantly simplifies the mathematical analysis compared to the more general case of a stochastic environment. We use our model to derive a combined stability condition including the effects of all of these mechanisms, which reveals both their individual contributions to stability, as well as their interactions.

2 Model

We assume that a winter allele W and a summer allele S are segregating at one locus in a randomly mating population. Each iteration of the model involves one round of random mating and juvenile recruitment to reproductive maturity. Some fraction of the copies of each allele are completely "protected" from selection, so that the allele frequencies within the protected fraction remain constant from one iteration to the next. The classic example of this form of protection is generational overlap (Chesson and Warner, 1981): if only a fraction $1 - f$ of reproductively mature individuals die and are replaced each round of juvenile recruitment, then alleles in the remaining fraction f experience no viability selection. Note that the particular copies of each allele that are protected may change between iterations. The environment alternates between summer and winter such that the per-iteration relative fitnesses of unprotected alleles take the values in Table 1.

For a polymorphism to be stable, both W and S alleles must increase in frequency over a full summer/winter cycle when rare. In the following, we assume that the winter allele is rare ($p_W \ll p_S \approx 1$, where p denotes allele frequency). The behavior of a rare summer allele is then obtained by swapping the S and

	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.

W labels. Since W is rare, almost all of its copies occur in heterozygotes, and almost all copies of S occur in homozygotes. The change in allele frequencies over one generation is thus given by

$$p'_W = [f + (1-f)\frac{w_{SW}}{\overline{w}}]p_W \qquad p'_S = [f + (1-f)\frac{w_{SS}}{\overline{w}}]p_S \tag{1}$$

where $\overline{w} = p_S^2 w_{SS} + 2p_S p_W w_{SW} + p_W^2 w_{WW}$ is population mean fitness. If there is no protection ($f = 0$), we have the usual $p'_W = \frac{w_{SW}}{\overline{w}} p_W$ and $p'_S = \frac{w_{SS}}{\overline{w}} p_S$.

Finally, we denote number of summer and winter iterations by i_S and i_W respectively. Using Eq. (1), and noting that $[f + (1-f)\frac{w_{SS}}{\overline{w}}] \approx 1$ because $w_{SS} \approx \overline{w}$, the condition for the rare winter allele to increase in frequency relative to the common summer allele over a complete summer/winter cycle is given by

$$\left[f + (1-f)\frac{w_{SW}(S)}{\overline{w}(S)}\right]^{i_S} \left[f + (1-f)\frac{w_{SW}(W)}{\overline{w}(W)}\right]^{i_W} > 1. \tag{2}$$

3 Results

3.1 Stabilizing mechanisms

In this section we compare four mechanisms that can stabilize polymorphism at a single locus: cumulative overdominance, reversal of dominance, protection from selection, and boom-bust population demography. We start by considering the first three of these, since in the absence of boom-bust population demography we

can make the simplifying assumption that the numbers of summer and winter iterations are constant. To further simplify, we begin by setting them equal $i_S = i_W$. It is then straightforward to show that Eq. (2) becomes (details in Appendix A)

$$(1 - d_S)a_S - d_W a_W < [f + (1 - f)d_S]d_W a_S a_W. \tag{3}$$

Below we use special cases of Eq. (3) to isolate the effects of cumulative overdominance, reversal of dominance, and protection from selection. We then extend Eq. (3) to make i_S variable rather than constant, and thus 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. (3). 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. (3) then simplifies to

$$a_S - a_W < d_S a_S a_W. \tag{4}$$

Eq. (4) shows that the rare winter allele can persist even if the summer allele is superior ($a_S > a_W$). Strong fluctuating selection is needed for stability, since the product of juvenile advantages $a_W a_S$ appears on the right hand side (i.e. the the stabilizing effect is second order in the juvenile advantages a_S and a_W). The stabilizing effect gets stronger with increasing summer dominance d_S.

Combining Eq. (4) with the corresponding condition for a rare summer allele (given by Eq. (4) 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. (3) can be written as

$$\frac{1-d}{d} a_S - a_W < d a_S a_W. \tag{5}$$

The right hand side of Eq. (5) is the same as the Eq. (4) case of cumulative overdominance. But the summer advantage a_S is now 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 may have. Unlike cumulative overdominance, which is second order in the juvenile advantages, reversal of dominance has a first order stabilizing effect (Fig. 1a, blue). This powerful effect arises because rare alleles are more often found in heterozygotes, thus gaining a major benefit from the fact 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 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

$$a_S - a_W < f a_S a_W \tag{6}$$

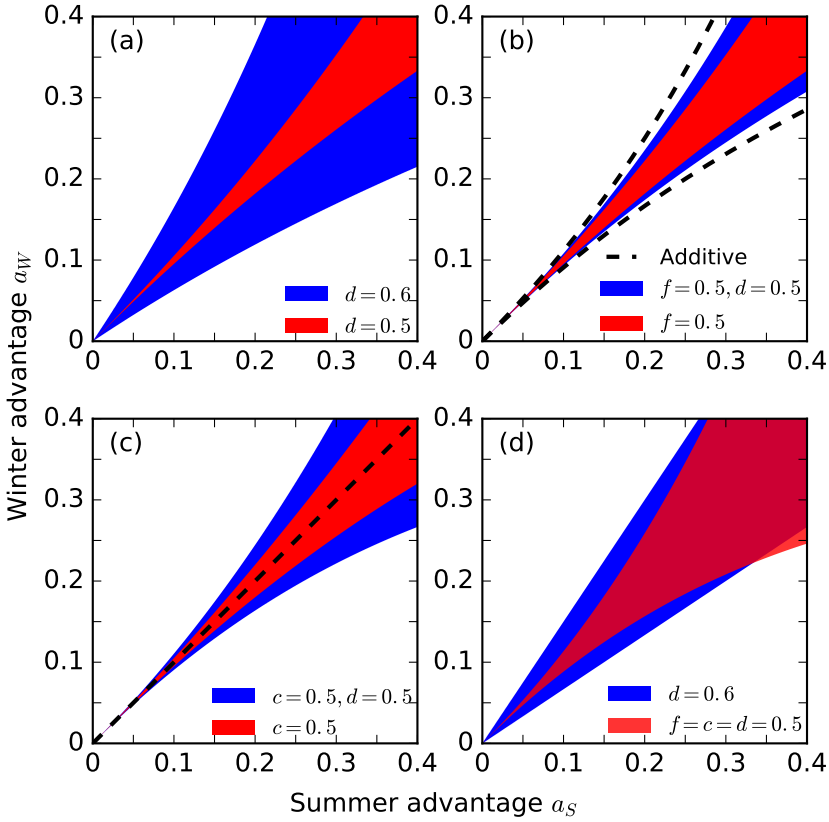

Figure 1: (a) Cumulative overdominance alone only stabilizes a small region (red; $d_S = d_W = 0.5$ in Eq. (4)), especially if selection does not fluctuate strongly (a_S and a_W are not large). Reversal of dominance creates a much larger region of stability (blue; $d = 0.6$ in Eq. (5)). (b) Protection from selection alone (from Eq. (6)) stabilizes a region with the same shape as cumulative overdominance, with magnitude set by f. The region stabilized by both (blue; $d_S = d_W = 0.5$ and $f = 0.5$ in Eq. (3) is smaller than if their effects were additive (dashed lines). (c) Boom-bust demography alone (red) is similar to cumulative overdominance, but is not symmetric (more of the stabilized region lies below than above the dashed line) since it hinges on the summer advantage a_S. (d) Reversal of dominance alone (blue; obtained by setting the right hand side of Eq. (2) to zero to artificially remove the simultaneous effect of cumulative overdominance) is effective at stabilizing alleles of any strength, but the combination of cumulative overdominance, protection from selection and boom-bust demography (red) is similarly effective for larger effect alleles despite the sub-additivity shown in (b).

This condition can be derived from scratch in a similar way to Eq. (3). Alternatively, we can simply observe that the haploid case is a special instance of our 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. (3)).

Eq. (6) is the same condition as Eq. (4), but with d_S replaced by f. Thus, like under 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 rare type is favored, and its growth therefore not limited by protection of the abundant type.

The combined effect of cumulative overdominance and protection from selection is smaller than their individual effects added together (Fig. 1b, blue). This can be seen from the fact that the first term on the right hand side of Eq. (3) is only $f + (1 - f)d_S$ with protection, not $f + d_S$, as would be the case if the stabilizing terms on the right of Eqs. (4) and (6) could simply be added together. The reason for this sub-additivity is that cumulative overdominance only affects unprotected allele copies.

3.1.3 Boom-bust demography

We now extend Eq. (3) to account for boom-bust demography by relaxing our previous assumption that $i_S = i_W$. Unequal but constant values of i_S and i_W do not induce frequency dependence and thus do not stabilize polymorphism. However, i_S can itself be a frequency-dependent variable if: (1) population density undergoes repeated boom-bust cycles; (2) population growth is density-regulated (i.e. growth slows due to crowding effects); and (3) selection in the

summer boom is driven by differences in absolute growth rates as the population expands from low density after the winter bust (i.e. "r-selection" predominates; as opposed to selection driven by competition).

Under these conditions, i_S is the number of iterations before population density begins to saturate and selection favoring the summer allele ceases. This induces negative frequency dependence because the common type determines the mean population growth rate. Thus, lower winter allele frequency implies more rapid population saturation, and hence fewer iterations of negative selection experienced by the winter allele. Conversely, lower summer allele frequency implies more iterations of positive selection on the summer allele (Fig. 2; Yi and Dean 2013).

In the simplest case of pure r-selection up to a fixed environmental carrying capacity without any kind of protection (this restriction is discussed further below), the abundance of summer alleles grows proportionally faster than that of winter alleles by factor $1 + a_S$. This implies that it takes proportionally $1/(1+a_S)$ fewer iterations to reach saturation when the summer allele is common compared to when it is rare. The number of summer iterations i_S then depends on frequency as follows (details in Appendix B)

$$i_{S|\mathrm{Srare}} \approx i_W(1 + ca_S) \qquad i_{S|\mathrm{Wrare}} \approx i_W(1 - ca_S), \tag{7}$$

where c is a constant of order 1/2 (discussed further below). 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. (3), giving (Appendix B)

$$(1 - d_S)a_S - d_W a_W < [f + (1 - f)d_S]d_W a_S a_W + c(1 - d_S)a_S^2. \tag{8}$$

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). Thus, the strength of the boom-bust mechanism is also second

order in the juvenile advantages, like cumulative overdominance and protection from selection, with the difference that the stabilizing term depends on the summer advantage only (Fig. 1c, red).

The strength of the boom-bust stabilizing mechanism is controlled by the constant $c = 1/(2 \ln F_{SS})$, where F_{SS} is the absolute per-iteration growth rate of summer homozygotes in the summer. This dependence of c on F_{SS} is a consequence of the discrete-time nature of our model. In the continuous time limit where each iteration represents a vanishingly small growth increment, $c \to 1/2$ and the boom-bust stability mechanism depends entirely on relative ratios between absolute Malthusian parameters (compare Yi and Dean 2013). However, in discrete time, faster per-iteration growth diminishes the proportional difference between $i_{S|\mathrm{Srare}}$ and $i_{S|\mathrm{Wrare}}$ (Appendix B). In practice, c will typically be of order 1/2 unless growth is extremely rapid (e.g. $c \approx 0.72$ in a population which doubles every summer iteration). We therefore set $c = 1/2$ in Fig. 1.

In the derivation of Eq. (8) we assumed no protection. Protection does not alter the dynamics of repeated expansion up to saturation that underpins the above analysis, and so Eq. (8) accurately conveys the essential features of the boom-bust mechanism. However, by assuming $f = 0$ we preclude analysis of the interaction between boom-bust demography and protection from selection. This is a complicated issue which requires a more sophisticated ecological model that would explicitly account for the particular form of protection involved (see Discussion).

3.2 Effectiveness of stabilization

In sections 3.1.1-3.1.3 we showed that the stabilizing effect of reversal of dominance is first order in the juvenile advantages, whereas the other three mechanisms are second order. This has consequences for the stabilization of alleles with weak versus strong fitness effects.

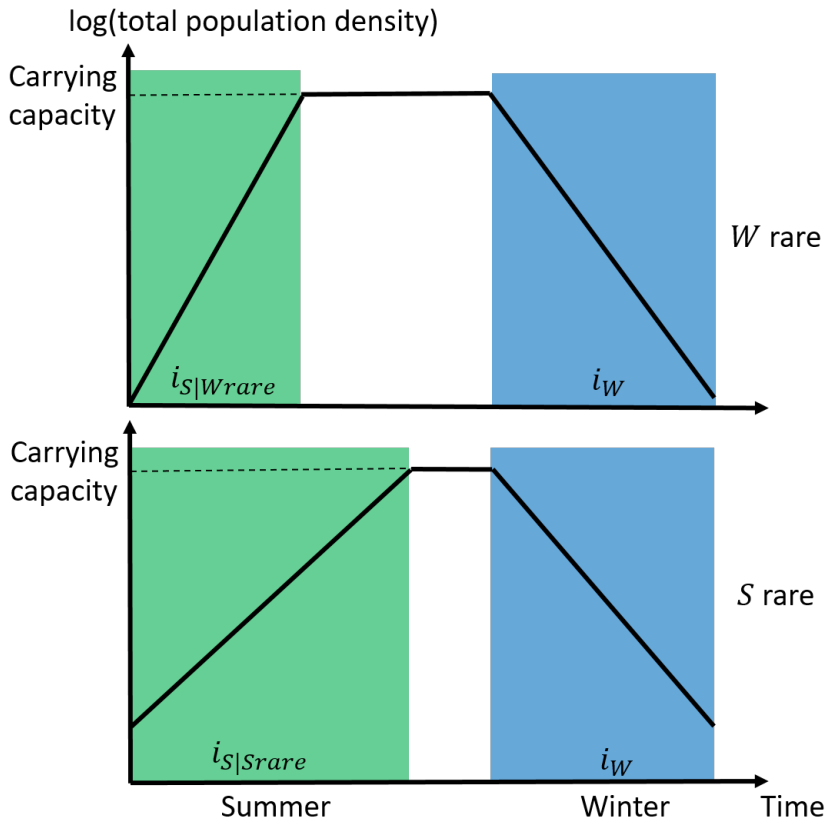

Figure 2: Illustration of a winter/summer boom-bust demographic cycle in a simplified model of exponential growth up to saturation in the summer, and exponential decline in the winter. The periods of selection in the summer and winter are marked with green and blue boxes respectively. Selection ceases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

The "effectiveness" of stabilization can be quantified in terms of the greatest difference in juvenile advantages compatible with stable polymorphism. However, 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 any juvenile advantages. 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. (4) 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 demography 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 be effective at stabilizing polymorphism. In Fig. 1d, the winter advantage can be as high as $a_W \approx 0.125$ for a summer advantage of $a_S = 0.1$ and still be compatible with balanced polymorphism (an "effectiveness" of 25%). 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.

To investigate further, we compute the juvenile advantage implied by a given seasonal allele frequency change (Fig. 3). Following the temperate *Drosophila* case, we set our given allele frequency change at 0.1 over the summer (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). 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. 3 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.

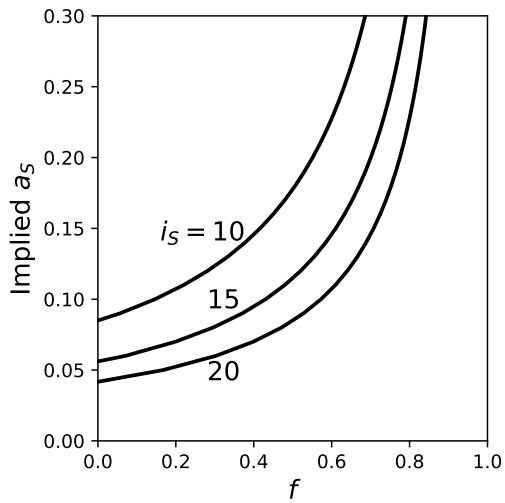

Figure 3: Juvenile advantages of at least ~ 0.05 per iteration are needed to produce a total juvenile allele frequency change of 0.1. Larger values are needed in the presence of protection, or if there are fewer rounds of juvenile recruitment each season. The change in summer allele frequency is given by $p'_S/p_S = f + (1-f)(w_{SW}(1-p_S) + w_{SS}p_S)/\overline{w}$ (analogous to Eq. (1), which only applies for common S).

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 (with the exception of the interaction between boom-bust demography and protection from selection; see below). 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. 3). 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.

4.1 Empirical tests and implications

Protection from selection and cumulative overdominance

The protection from selection mechanism is probably widespread, since there will likely be some amount of protection from the overlapping generations of iteroparous organisms. However, protection from selection will not be effective at stabilizing polymorphism unless selection is also strong, as measured

by the juvenile advantages a_S and a_W. Similar considerations apply for cumulative overdominance; the required incomplete dominance is also likely to be widespread, but will not be effective at stabilizing polymorphism unless selection is strong. The strong selection requirement presumably limits the prevalence of these mechanisms as a stabilizers of polymorphism. However, as we have seen in Sec. 3.3, *Drosophila* data are compatible with juvenile advantages being surprisingly large, particularly if the fraction of protected alleles f is appreciable. Specifically, Fig. 3 suggests that juvenile advantages of order ~ 0.1 are compatible with the magnitude of allele frequency oscillations; this is strong enough for mechanisms other than reversal of dominance to stabilize polymorphism.

Estimating the magnitude of f is challenging. In many models with protection, generational overlap is the primary form of protection, fecundity remains constant with age, and total population density is constant (Chesson and Warner, 1981; Ellner and Hairston, 1994; Svardal et al., 2015). The strength of protection f is then simply the fraction of surviving adults each round of juvenile recruitment. With this simple model model in mind we can get a rough estimate of of the magnitude of f in wild *Drosophila* from laboratory measurements. Female fecundity peaks ≈ 5 days after reaching reproductive maturity but egg laying continues up to 20 days after which female survivorship declines rapidly (Le Bourg and Moreau, 2014). We approximate this as death occurring at 20 days. Assuming that it takes 10 days to develop from an egg to reproductive maturity, this means that females persist for roughly two rounds of juvenile recruitment under laboratory conditions. This corresponds to a protection due to overlapping generations of $f = 0.5$. This number is probably an overestimate since females in the wild are subject to additional sources of mortality such as predation and parasitism.

In reality, protection is more complicated. Adults may also experience some selection, e.g. due to predation/parasites. In this case, protected alleles only experience weakened negative selection, not complete protection; $f + (1 - f)\frac{w}{\overline{w}}$

in Eq. (1) would then be replaced by $f\frac{w_P}{\overline{w_P}} + (1-f)\frac{w_U}{\overline{w_U}}$ where P and U stand for "protected" and "unprotected", respectively. Additional complications arise in an expanding population. For instance, the strength of protection may depend on how rapidly the population is growing; even if the proportion of surviving adults is large, they will only constitute a small fraction of the population if a large number of juveniles is recruited to adulthood each iteration. Other forms of protection include maternal effects, which can confer protection because, in any given iteration, some fraction of unfavored alleles will have a favored mother (e.g. the heterozygote offspring of a summer homozygote in the summer). We would then need to distinguish between the possible parental combinations that an allele might experience (Wolf and Wade, 2016). The development of population genetic methods to quantify protection from selection is needed.

Boom-bust demography

Boom-bust demography is distinguished by its reliance on crowding effects. While crowding effects feature prominently in organisms with relatively stable demography, the presence of strong crowding effects is less certain in populations which undergo cyclical collapses in population density. A relatively simple way to test for the presence of stabilization driven by boom-bust demography would be to alleviate the effects of crowding by artificially constraining density e.g. via culling. If boom-bust demography is indeed stabilizing polymorphism, we would then expect temporally-averaged allele frequencies to shift (potentially even losing the polymorphism), as a result of the weakening of the boom-bust demography rarity advantage.

Reversal of dominance

Reversal of dominance is distinguished by its stabilizing effectiveness: it is an order of magnitude stronger than cumulative overdominance, protection from selection and boom-bust demography. Among the mechanisms considered here,

reversal of dominance is unique in being insensitive to the magnitude of the juvenile advantages (Sec. 3.2). Thus, we might be able to test for the presence of reversal of dominance stabilization by experimentally weakening the juvenile advantages a_S and a_W by similar proportions. We would then expect to only see a reduction in the amplitude of allele frequency oscillations, with comparatively little change in temporally-averaged allele frequencies. The reason for this is that the temporally-averaged allele frequency is set by a balance between the superior juvenile advantage of one allele and the rarity advantage of the other; under reversal of dominance these both scale with the juvenile advantage. By contrast, under cumulative overdominance, protection from selection and boom-bust demography, the rarity advantage rapidly disappears for smaller a_S and a_W, and we would expect to see the allelic superiority overwhelming it if we weaken selection.

Multi-locus polymorphism

Our analysis has considered the simple case of two alleles segregating at a single 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. 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; 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

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 not addressed two important aspects of how frequency-dependence is induced by crowding. First, we have not evaluated how sensitive Eq. (7) is to the simplifying assumption of growth without crowding followed by complete saturation in the summer (Fig. 2). In a more realistic model, crowding effects will gradually become more important as population density increases. The stabilizing effect of boom-bust demography fundamentally revolves around the total amount of growth that each genotype experiences over the summer (see Yi and Dean 2013). We therefore expect that more realistic models will yield similar conclusions to ours provided that crowding effects are strong by the end of the growth season, regardless of whether growth can be regarded as "saturated". Second, we have not considered how density-dependent selection within the boom period might affect our results; this could either weaken or strengthen the effect of boom-bust demography depending on which allele benefits from higher densities. A full analysis of these two complications requires us to model absolute genotypic abundances, explicitly incorporating the effects of crowding as a regulator of population density and mediator of competition. To account for the role of protection in an expanding population, we would also require a more explicit model of the protection mechanism. The variable-density territorial contest model of Bertram and Masel (2018), which has overlapping generations, is one possibility for analyzing exploring some of these issues.

We have restricted our attention to temporal variation, and hence have not attempted to explore spatial variation or phenotypic variation within genotypes (individual variation), or the important question of how different sources of variation interact. The latter question is the focus of Frank and Slatkin (1990) and Svardal et al. (2015). Our restriction to temporal variation is motivated by the example of pervasive seasonally oscillating polymorphism in *Drosophila* (Machado et al., 2018). This empirical system poses a theoretical problem because previous studies have raised doubts about the stabilizing potential of

temporal variation (see Introduction). The spatial case is less interesting in this respect, because it is generally accepted that spatial variation has considerable stabilizing potential. The reason for this difference is that some copies of alleles in spatially variable environments may never experience unfavorable locales, whereas all allele copies must be able to survive unfavorable periods under temporal variation (Hedrick, 2006).

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

This points to a broader divide between population genetic and more phenotypic approaches (such as adaptive dynamics) to the study of genetic variation. Adaptive dynamics approaches typically view variation through the lens of evolutionary branching, which implies disruptive selection at the phenotypic level. One consequence of disruptive selection is that fitness-associated genetic variation is expected to become concentrated at a few loci, not dispersed over many, because recombination is more likely to produce less fit intermediate phenotypes when genetic variation is dispersed (Kopp and Hermisson, 2006; van Doorn and Dieckmann, 2006; Svardal et al., 2015). The population genetic approach does

not require phenotypic disruptive selection, and predicts no tendency for genetic variation to be concentrated (Wittmann et al., 2017). However, population genetic approaches generally do not specify the phenotypic basis of selection at all. This quickly becomes problematic when trying to account for ecological factors, as we have seen in the case of boom-bust demography. There is therefore a need to better integrate the population genetic and phenotypic approaches.

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Appendix A: Details of diploidy and protection from selection conditions

Here derive the condition for stable polymorphism under the combined effects of diploid Mendelian inheritance and protection from selection, Eq. (6). Recall that this condition assumes $i_S = i_W$, and so we can take the i_W'th root to remove the exponents in Eq. (2). Multiplying by $\overline{w}(S)\overline{w}(W)$, Eq. (2) can thus be written as

$$[f\overline{w}(S) + (1-f)w_{SW}(S)]\,[f\overline{w}(W) + (1-f)w_{SW}(W)] > \overline{w}(S)\overline{w}(W). \tag{9}$$

Substituting from Table 1 we have,

$$[f(1+a_S) + (1-f)(1+d_S a_S)]\,[f + (1-f)(1+d_W a_W)] > 1 + a_S, \tag{10}$$

which can be simplified to

$$[1 + (f + (1-f)d_S)a_S]\,[1 + (1-f)d_W a_W] > 1 + a_S. \tag{11}$$

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

$$(f-1)a_S + (1-f)d_S a_S + (1-f)d_W a_W + (1-f)(f + (1-f)d_S)a_S d_W a_W > 0. \tag{12}$$

Dividing by $(1-f)$ then gives

$$(d_S - 1)a_S + d_W a_W + (f + (1-f)d_S)a_S d_W a_W > 0, \tag{13}$$

which yields Eq. (3).

Appendix B: Details of the boom-bust condition

We consider a model of pure r-selection in which the total change in population abundance from the beginning of the summer until reaching its environmental carrying capacity is a fixed factor of D (see Yi and Dean 2013 for a similar

approach). The absolute growth rates associated with each genotype prior to reaching carrying capacity will be denoted F; for example the abundance of a winter allele that is rare and hence restricted to heterozygotes grows according to $n'_{SW} = F_{SW} n_{SW}$ over an iteration. For simplicity, we assume that there is no protection, because then from Eq. (1) we simply have $F_{SW}/\overline{F} = w_{SW}/\overline{w}$ (and similarly for the other genotypes) i.e. the F are proportional to the corresponding values w.

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

$$\begin{aligned} i_{S|\mathrm{Srare}} &\approx \frac{\ln D}{\ln F_{SS} - a_S} \\ &= \frac{\ln D}{\ln F_{SS}} \frac{1}{1 - a_S/\ln F_{SS}} \\ &\approx i_{S|\mathrm{Wrare}}(1 + a_S/\ln F_{SS}). \end{aligned} \tag{14}$$

Defining $i = (i_{S|\mathrm{Srare}} + i_{S|\mathrm{Wrare}})/2$ as the "baseline" number of summer iterations, we therefore have $i_{S|\mathrm{Srare}} \approx i(1 + ca_S)$ and $i_{S|\mathrm{Wrare}} \approx i(1 - ca_S)$ to first order in a_S, where $c = 1/(2 \ln F_{SS})$.

As a side note, the reason that c is a decreasing function of F_{SS} is that the summer advantage applies to absolute growth factors in discrete time (i.e. $F_{SS}/F_{WW} = 1 + a_S$). Thus, since $(F_{WW})^{i_{S|\mathrm{Srare}}} = D = (F_{SS})^{i_{S|\mathrm{Wrare}}}$, we have $1 + as = F_{SS}^{\frac{i_{S|\mathrm{Wrare}} - i_{S|\mathrm{Srare}}}{i_{S|\mathrm{Srare}}}}$. In other words, for a given summer advantage a_S, a faster absolute growth rate translates into a smaller proportional difference in the number of iterations of selection between the two frequency regimes.

For simplicity, in Eq. (7) we assume symmetry between the seasons, such that the winter has the same number of iterations as the baseline number of

summer iterations, i.e. $i_W = i$ with $i_S = i_W$ in the case where $a_S = 0$. In the asymmetric case where either summer or winter is intrinsically longer, a different region of juvenile advantages can permit stable polymorphism. For instance, the summer advantage must be larger for a given winter advantage if $i_W > i$. But this asymmetry does not affect the overall magnitude of the stabilized region, because constant differences between i_S and i_W do not introduce frequency dependence.

Taking the i_W'th root of Eq. (2), our stability condition for a rare winter allele can thus be written analogously to Eq. (11) as

$$[1 + (f + (1 - f)d_S)a_S]^{i_S/i_W} \, [1 + (1 - f)d_W a_W] > (1 + a_S)^{i_S/i_W}, \qquad (15)$$

where $i_S/i_W = 1 - ca_S$. We then apply the generalized binomial theorem: $(1 + x)^r = 1 + rx + \frac{r-1}{2!}x^2 + \ldots$. This implies $(1+a_S)^{1-ca_S} = 1 + (1-ca_S)a_S + O(a_S^3)$, and similarly $[1 + (f + (1 - f)d_S)a_S]^{1-ca_S} = 1 + (f + (1 - f)d_S)(1 - ca_S)a_S + O(a_S^3)$. Neglecting third order terms in a_S, Eq. (15) is thus the same as Eq. (11), but with a_S replaced by $(1 - ca_S)a_S$. The same steps used to obtain Eq. (3) from Eq. (11) (Appendix A) will therefore yield Eq. (3) with a_S replaced by $(1 - ca_S)a_S$. In the resulting inequality, the ca_S contribution on the right hand side is $O(a_S^3)$ and can be neglected, and we move the ca_S contribution on the left hand side to the right to obtain Eq. (8).

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