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A central role for boom-bust cycles in maintaining genetic variation in fluctuating environments

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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 natural *Drosophila* populations. One possible explanation is that polymorphism is stabilized by an alternating summer-winter selection regime. The general principle that fluctuating environments can promote coexistence is widely accepted, often in the guise of the "storage effect", yet little has been done to evaluate and compare coexistence mechanisms under seasonally alternating selection coupled with large seasonal variation in population size. Here we distinguish two general mechanisms, which we call "density-regulated growth", and "protection from selection". We contrast and compare these mechanisms, both in terms of the underlying biology, and in terms of their capacity to stabilize coexistence. We clarify their connection to the storage effect, which is still sometimes confusingly identified with protection from selection. We also clarify the role of overlapping generations as a form of protection. We find that density-regulated growth is a powerful stabilizer under conditions in which protection from selection might be weak.

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1 Introduction

A longstanding question in evolutionary genetics is whether genetic variation is stabilized by selection (Dobzhansky's "balance view"), or whether it is intrinsically unstable and maintained in a state of continual turnover by mutation (Morgan and Muller's "classical view", and the view of neutral theory; Barton et al. 2007, pp. 34). DNA sequence data from natural *Drosophila* populations has revealed an important role for both (Gloss and Whiteman, 2016). While deleterious mutations contribute significantly to fitness variation in Drosophila (Charlesworth, 2015), many polymorphic loci appear to be undergoing long-term, stable and adaptive oscillations in allele frequency coinciding with seasonal variation in the environment and population size (Bergland et al., 2014).

Although there is some recognition that environmental variability can promote coexistence, the mechanisms underlying the apparent prevalence of balancing selection in *Drosophila* are not well understood (Messer et al., 2016). For a long time population genetics viewed fluctuating selection as akin to a form of drift, and therefore as a factor which destroys variation (Gillespie, 1994, pp. 228). This view persisted even though genotypic coexistence for asexual haploids parallels species coexistence in community ecology, and ecologists have long entertained the idea that environmental variation promotes species coexistence (Hutchinson, 1961; Chesson and Warner, 1981; Chesson, 2000; Li and Chesson, 2016). Even Gillespie's (1994) lengthy defense of balancing selection revolved around diploidy, rather than harvesting

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the ecological literature and appealing to selection alone. More recently, the ecological "storage effect", which is thought to promote coexistence in variable environments under quite general conditions (Chesson, 2000), has been applied to genotypes (Ellner and Hairston, 1994; Svardal et al., 2015), although as we will see, considerable confusion surrounds the term. Compounding these difficulties, population genetics has historically paid little attention to rapid adaptation (Messer et al., 2016) and ecological factors such as dynamic population size.

Here we evaluate and compare two mechanisms which could promote coexistence in variable environments under a broad range of conditions, including in natural *Drosophila* populations. The first, borrowed from ecology, is that a proportion of each genotype's individuals may experience less intense selection than the rest. This occurs, for instance, if adults are long-lived and iteroparous, and differential survival is more pronounced in juveniles. We call this "protection from selection". The second mechanism is repeated, density-regulated population expansion, as occurs in serial transfer experiments (Yi and Dean, 2013). We call this "density-regulated growth". We focus on the haploid case, since diploidy has more to do with allelic assortment than selection, but we will also touch on the role of diploidy.

These two distinct mechanisms, both of them broadly applicable, exemplify the potential for confusion surrounding the storage effect. Protection from selection is sometimes identified with the storage effect (Ellner and Hairston, 1994; Yi and Dean, 2013; Svardal et al., 2015), and in its original form the storage effect was indeed illustrated using a model of protection from

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selection (Chesson and Warner, 1981). However, the storage effect has since come to mean something much more general (Chesson, 2000). Protection from selection is clearly a different mechanism from density-regulated growth, since only the former requires selection to vary, given a specific environment, within each genotype/species, whereas only the latter is intrinsically tied to population expansion and saturation. Nevertheless, in its current, more general form, the storage effect encompasses both of these mechanisms (Li and Chesson, 2016). Here we clarify how these three concepts are related.

We start by giving a simple, intuitive analysis of protection from selection and then also examine the case of protection due to incomplete dominance in diploids (sections Protection from selection and Geometric mean heterozygote advantage). We then discuss the storage effect in its original lottery model and modern forms (Sec. The storage effect), followed by density-regulated growth in a model of microbial growth under serial transfer (Sec. Density-regulated growth) and how it relates to the storage effect (Sec. Density-regulated growth as a form of the storage effect). With the definitions and modes of operation of these coexistence mechanisms clear, we then analyze a simple model that has both density-regulated growth and protection from selection, to compare their effects (Sec. Density-regulated growth with protection).

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2 Stable coexistence mechanisms

2.1 Protection from selection

We consider two types a and b with frequencies p_a and $p_b = 1 - p_a$, and suppose that a fraction f of the population is protected from selection, such that the usual change in type frequencies after one iteration $p'_a = [w_a/\overline{w}]p_a$ is replaced by

$$p'_a = [f + (1 - f)w_a/\overline{w}]p_a, \tag{1}$$

where w_a and w_b are frequency-independent and $\overline{w} = p_a w_a + p_b w_b$ is population mean w. The environment alternates between favoring each type, such that their relative fitnesses are $w_a = 1 + s_a$ and $w_b = 1$ in one environmental iteration, then $\hat{w}_a = 1$ and $\hat{w}_b = 1 + s_b$ in the next (the hat distinguishes between iterations).

Coexistence requires negative frequency dependence in fitness measured over a full environmental cycle of two iterations (i.e. in geometric mean fitness). When type a is rare ($p_a \to 0$), it grows by a factor $f + (1 - f)w_a = 1 + (1 - f)s_a$ when favored, and declines by a factor $f + (1 - f)/\hat{w}_b = f + (1 - f)/(1 + s_b)$ when disfavored. p_a will increase if the product of these factors is greater than 1, which implies (additional working is given in Supplement A)

$$s_b - s_a < f s_a s_b, \tag{2}$$

where $0 \leq f < 1$. This shows that protection from selection intrinsically favors rare types; even if b is "superior" in the sense that $s_b > s_a$, the

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rare a type can co-exist if s_a and s_b are sufficiently large relative to their difference. The analogous requirement for b to increase when rare is obtained by swapping a and b labels in Eq. (2); together these define a region of coexistence for a given f (Fig. 1).

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 it is favored due to sheer numerical advantage. Protection directly 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 it is favored, with protection or without.

Eq. (2) highlights the crucial role of the intensity of environmental variation in stabilizing coexistence via protection from selection (Chesson and Warner, 1981), as measured by the magnitude of $s_a s_b$. Note that s_a and s_b are selection coefficients over environmental iterations, i.e. over the unit of time on which the environment fluctuates. In other words, coexistence relies on relatively large swings in frequency over each environmental iteration.

The preceding paragraphs capture the key intuitions behind protection from selection. The extension to a general stochastic environment does not introduce any substantially new concepts, but is considerably more mathematically involved. The general practice has been to treat environmental variation as a stochastic process (Chesson and Warner, 1981; Gillespie, 1994) rather than considering the much simpler cyclical case (although see Gulisija et al. 2016).

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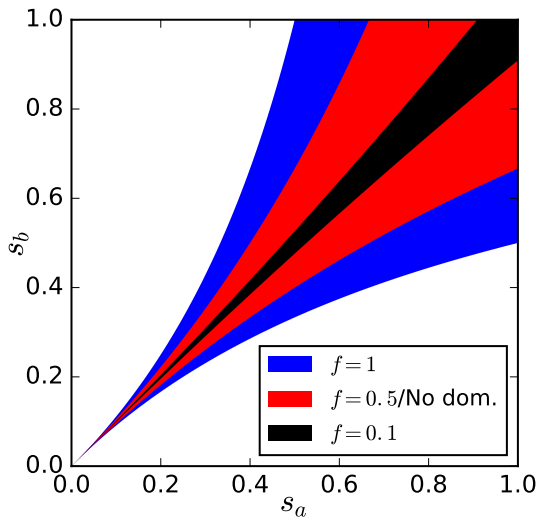

Figure 1: Protection from selection stabilizes coexistence in a region $s_a/(1+fs_a) < s_b < s_a/(1-fs_a)$. Diploidy alone (without dominance) can be viewed as a form of protection from selection at the allelic level with $f = 0.5$. The limit of maximal protection from selection $f \to 1$ in Eq. (2) is included for comparison, although strictly speaking any types will co-exist if $f = 1$ exactly.

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2.2 Geometric mean heterozygote advantage

Our example of protection from selection in the previous section may seem somewhat contrived for illustrative purposes, but it is in fact closely related to selection in diploids with incomplete dominance. Considering the canonical example of a single locus with two alleles a and b under random mating, the change in the frequency of a is

$$p'_a = [f w_{ab}/\overline{w} + (1-f) w_{aa}/\overline{w}] p_a \tag{3}$$

where $f = 1 - p_a$ is the fraction of a alleles in heterozygotes. Unlike Eq. (1), f now depends on frequency, is different for the b allele (the fraction of b alleles in heterozygotes is $1 - p_b = 1 - f$), and protected individuals still experience selection. However, since dominance is incomplete, alleles in heterozygotes experience weaker selection compared to those in homozygotes, and a similar argument as given above applies.

The environment alternates such that the homozygote fitnesses are $w_{aa} = 1 + s_a$ and $w_{bb} = 1$ in one environmental iteration, then $\hat{w}_{aa} = 1$ and $\hat{w}_{bb} = 1 + s_b$ in the next. If there is no dominance ($w_{ab} = (w_{aa} + w_{bb})/2$), then the condition for p_a to increase when a is rare is (Supplement A)

$$s_b - s_a < \frac{1}{2} s_a s_b. \tag{4}$$

The coexistence conditions if there is dominance are a little more complicated because there are two additional parameters (a dominance co-efficient for both environmental iterations), but the basic result remains that protection in heterozygotes stabilizes polymorphism. The case of no dominance brings

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this out particularly clearly, since Eq. (4) is akin to a constant complete protection of $f = 1/2$ in the simple haploid example from Sec. Protection from selection.

2.3 The storage effect

We now describe the original version of the storage effect, how it relates to Eq. (1), and the more general current form of the storage effect.

The original version of the storage effect was studied in the context of reef fishes using a lottery model (Chesson and Warner, 1981). In the classic lottery model, the reproductively mature individuals (adults) in a community produce dispersing juveniles which compete for the territories made available by the death of adults. The community frequency of species i's adults after one environmental iteration is given by

$$p_i' = [(1 - d_i) + \overline{d}\beta_i/\overline{\beta}]p_i \tag{5}$$

where β_i measures how successful species i is at securing new territories (the number of juveniles produced multiplied by a measure of juvenile competitive ability), d_i is per-capita adult mortality, and the population mean adult mortality rate $\overline{d}$ measures the amount of territory available for juveniles in that iteration.

It can be seen from Eq. (5) that the classic lottery is almost identical to Eq. (1). If all species have the same mortality rate $d_i = d$, then they are identical: β replaces w and $f = 1 - d$. Thus, the classic lottery model can be seen as a version of Eq. (1) where the species/genotypes can be protected by

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different amounts. Due to the close connection between adult mortality and protection in the lottery model, the classic storage effect is often phrased in terms of overlapping generations ("storage of adults").

The current form of the storage effect is much more general (Chesson, 2000). The setup is as follows. Species growth rates r_i are assumed to depend on two factors: "environmentally-dependent parameters" E_i, which include demographic parameters such as birth rates and which are independent of species densities in a community; and "competition" C_i, which depends on the E_i and species densities, and measures the reduction in growth rate due to the presence of other individuals (Chesson, 1994, pp. 234). The subscript i indicates that different species have different demographic parameters and may experience competition differently. The storage effect is then defined as a temporally-averaged rarity advantage induced by the combination of: (1) different types must be favored in different environmental conditions; (2) there must be nonzero temporal covariance between E_i and C_i; and (3) r_i must be less sensitive to competition in unfavorable environments compared to favorable environments, such that the detrimental effects of competition during unfavorable periods are partly mitigated ("buffered population growth"). Requirement (3) can be expressed mathematically as $\frac{\partial^2 r_i}{\partial C_i \partial E_i} < 0$ (Chesson, 1994), i.e. the detrimental effects of competition decline with decreasing E_i. An alternative, slightly simpler way to define the general storage effect is to combine (2) and (3) into a single requirement that the temporal covariance between E_i and C_i depends on species densities in such a way that it is greater for abundant species compared to rare species

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(Peter Chesson, personal communication, June 2016).

The general version of the storage effect has the concept of competition at its heart. Qualitatively, competition refers to mutually negative effects between or within species (or genotypes) due to shared limiting resources and/or direct interference (see Abrams and Cortez 2015 for a recent summary). The general storage effect needs much more than this qualitative definition: it needs a formal quantification of competition. This is considerably more challenging. For example, if we were to simply define (or measure experimentally) a "net competition" quantity C_{ij} as the differential change in r_i due to the addition of an individual of type j to the community (or population), this would aggregate the effects of all of the interactions between species/genotypes, both positive (non-competitive) and negative (competitive). A shared predator can also show up in this term as "apparent competition" via mutually negative terms, despite not meeting intuitive mechanistic expectations for the term "competition" (Holt, 1977; Chesson, 1994). What is more, there is no clear definition for the timescale over which the change in r_i should be assessed; below (Sec. Density-regulated growth as a form of the storage effect), we shall see that the timescale is a variable not a fixed parameter for some coexistence mechanisms, complicating the quantitative interpretation of competition. These issues may not be apparent in special cases defined by simple models, but there is clearly scope for interpretation and ambiguity.

In sum, the general version of the storage effect is a phenomenological umbrella term for a form of fluctuation-dependent coexistence. This is useful

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for distinguishing among broad classes of coexistence mechanism (Chesson, 2000). However, it is less helpful for distinguishing coexistence drivers at a more mechanistic level, because of the potential ambiguity of the phenomenological "competition" quantity, and because the conditions placed on this quantity are expressed as statistical covariances that might arise from a potentially unlimited variety of mechanistic causes. Protection from selection is also phenomenological in the sense that many different biological mechanisms could lead to weakened selection on a fraction of a genotype's or species' individuals. Nevertheless, the connection from underlying biological mechanisms to protection from selection is more transparent than to the statistical covariances of the storage effect (Fig. 2).

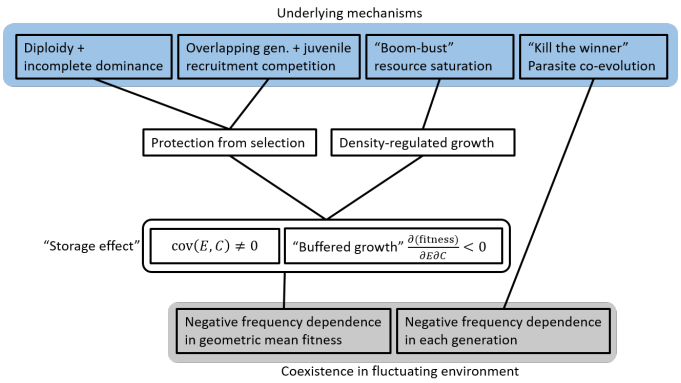

Figure 2: Schematic of the relationship between the mechanisms underlying coexistence when genotypes/species respond differently to a fluctuating environment, shown as a hierarchy from more mechanistic (top) to more phenomenological (bottom).

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2.4 Density-regulated growth

We now discuss our second general coexistence mechanism, which arises from repeated population expansion under density-regulated growth (Yi and Dean, 2013). We consider a serial transfer experiment, where two genotypes a and b grow exponentially up to saturation (when growth immediately ceases), followed by dilution to begin the next round of growth. We keep track of the type abundances immediately after dilution n_a, such that

$$n'_a = W_a n_a, \tag{6}$$

and similarly for b, where $W_a = De^{g_a T}$ is the post-dilution growth factor, g_a and g_b are environmentally-dependent Malthusian growth rates, and $D < 1$ is the dilution factor. T is the time spent growing, which depends on the initial genotype abundances and the environment. The growth conditions alternately favor one type or the other, such that $g_a/g_b = 1 + x_a$ in one growth iteration, then $\hat{g}_b/\hat{g}_a = 1 + x_b$ in the next.

Even though the growth rates g_a and g_b are frequency-independent, there is an intrinsic advantage to being rare. The reason is simple: a rare genotype spends more time growing when it is favored because the overall growth time T is determined by the abundant genotype, which takes longer to reach saturation when it is not favored (Yi and Dean, 2013). For a to increase in frequency relative to b over a full environmental cycle, we require

$$W_a \hat{W}_a - W_b \hat{W}_b > 0. \tag{7}$$

If a is rare ($n_a \ll n_b$), then $T = \ln(1/D)/g_b$. Here $1/D$ is the overall factor

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that the population grows by each cycle, and $\ln(1/D)$ is proportional to the corresponding number of doublings (since $\log_2(1/D) = \ln(1/D)/\ln 2$). Substituting this expression for T into Eq. (7) gives

$$x_b - x_a < x_a x_b. \tag{8}$$

While Eq. (8) appears analogous to Eq. (2) with $f = 1$, it highlights an important distinction between protection from selection and density-regulated growth. In the protection case, coexistence depends on the magnitude of the selection coefficients s_a and s_b over one environmental iteration (Sec. Protection from selection). By contrast, Eq. (8) depends on proportional differences in instantaneous growth rates x_a and x_b, but not on the overall amount of growth which occurs. The analogue of a per-iteration selection coefficient for the a type is not x_a but $\ln(1/D)x_a$. Thus, unlike protection from selection, coexistence can be stabilized by density-regulated growth even if the magnitude of selection per iteration is small e.g. even if only a small amount of fresh resources is added in the process of dilution to start each growth cycle.

Eq. (6) is a highly simplified model of microbial growth. Is the coexistence condition Eq. (8) sensitive to this simplification? Intuitively, if we had instead assumed gradual resource consumption up to a fixed iteration time, then a similar argument should apply: the abundant type depletes the common resource pool more slowly when disfavored, so that the rare type gets more time to exploit its advantageous iterations before resources are depleted.

To add rigor to this intuition, we evaluated the density-regulated growth mechanism in an explicit resource consumption model (Supplement B). In-

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stead of Malthusian growth parameters, g_a and g_b are constants measuring resource uptake rates per capita and per unit of unconsumed resource. Total population growth is then approximately logistic when one type dominates. In the case that each iteration is long enough that growth has approximately ceased by the end (of course, complete cessation never occurs under logistic growth), the region of co-existence is given by Eq. (8) as before. Therefore, the sudden saturation of Yi and Dean's (2013) model is not needed for density-regulated growth to operate as a coexistence mechanism.

In fact, saturation is not needed at all in the explicit resource consumption model. When saturation does not occur every iteration, the b type consumes more resources in its favorable iterations, and Eq. (8) is replaced by

$$\alpha x_b - x_a < x_a x_b, \tag{9}$$

where $\alpha > 1$ is the ratio of the number of b type doublings when it is favored to when it is not (Supplement B). Eq. (9) only precludes coexistence for $x_a < \alpha - 1$; otherwise coexistence is possible. The magnitude of α depends on the variation in the abundant b type's resource uptake rates between iterations (i.e. over time), as well as how much extra b-type growth is possible before saturation occurs. In particular, if the iteration time is so small that growth is still exponential at the end of each iteration, we have $\alpha \approx \hat{g}_b/g_b$. Thus, even in this extreme non-saturation case, coexistence is only precluded if the proportional advantage of the a type x_a is smaller than the proportional variation in the b type's uptake rate between iterations $\hat{g}_b/g_b - 1$. Of course, in general this limitation on the variation in uptake rates over time need not

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hold, in which case saturation can play a crucial stabilizing role by capping the amount of extra growth possible for the abundant type.

2.5 Density-regulated growth as a form of the storage effect

Given the generality of the storage effect (Sec. The storage effect), it is perhaps not surprising that coexistence due to density-regulated growth can be viewed as a special case (Li and Chesson, 2016). To do so, it is necessary to define environmentally-dependent parameters E_i and competition C_i in this context. The log growth rate per cycle implied by Eq. (6) is

$$\begin{aligned} r_a = \ln n'_a - \ln n_a &= g_a T + \ln D, \\ &= -g_a C + \ln D, \end{aligned} \tag{10}$$

where in the second line "competition" has been identified as $C = -T$ (following Li and Chesson 2016; we discuss this choice further below), and is the same for both types. The environmentally-dependent parameters are g_a and g_b.

Under these definitions, conditions (1-3) for the storage effect are satisfied. (1) The genotypes are favored in alternate cycles. (2) There is nonzero covariance between C and the two growth rates, because C is a function of T which is in turn a function of the growth rates. (3) Population growth is "buffered", since C is multiplied by g_a in Eq. (10), and so the effects of competition in unfavorable iterations are partly mitigated by the correspondingly low value of g_a. Mathematically, the rare a type increases in frequency

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if $\langle r_a - r_b \rangle > 0$, where angle brackets denote the mean with respect to time, and Eq. (10) implies

$$\langle r_a - r_b \rangle = (\langle g_a \rangle - \langle g_b \rangle) \langle C \rangle - (\mathrm{cov}(g_a, C) - \mathrm{cov}(g_b, C)) . \tag{11}$$

Here $\mathrm{cov}(g_a, C) = \langle g_a C \rangle - \langle g_a \rangle \langle C \rangle$ is the temporal covariance between g_a and C. The storage effect is reflected in a positive contribution to $\langle r_a - r_b \rangle$ from the covariance terms on the right; $\mathrm{cov}(g_a, C)$ is negative, because a larger than average g_a implies longer than average T, and hence smaller than average C, and similarly, $\mathrm{cov}(g_a, C)$ is positive.

The example of density-regulated growth reveals how the general form of the storage effect, though it does indeed encompass density-regulated growth, can mask important distinctions between coexistence mechanisms. The nominal "storage" in this case is the accumulated total biomass of each type (Li and Chesson, 2016); quite different from the presence of a protected subset of each type, like long-lived adults, or a seed bank, or heterozygotes. Replacing the time for growth T by $-C$ only serves to conceal a concrete biological mechanism behind the broad banner of "competition", which in general can be quantified in many different ways (Sec. The storage effect). Note that in terms of C, there is less competition if there are more resources at the start of a growth cycle and thus more time for depletion to take place (keeping the intrinsic competitive behaviors of each type the same), even though this could potentially produce more dramatic changes in frequency.

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3 Density-regulated growth with protection

We now compare the effects of protection from selection and density-regulated growth on coexistence under seasonal environment variation. We extend the serial transfer dynamics of (Yi and Dean, 2013), described by Eq. (6), such that part of the population is protected from selection. At the start of each growth cycle, a fraction f of the population is set aside and literally "stored" in stasis. The remaining fraction $1-f$ undergoes exponential growth to saturation. To initiate the following cycle, a fraction D of the population which grew to saturation is combined with the stored individuals and transferred to a fresh medium. A fraction f of this combined population is stored, and so on. The resulting dynamics are given by

$$n_a' = [f + (1-f)W_a]n_a. \tag{12}$$

Here W_a is analogous to the relative selection factor $w_a/\overline{w}$ in Eq. (1). For a to increase in frequency relative to b over a full environment cycle, we need (Supplement A)

$$f\phi + (1-f)\psi > 0, \tag{13}$$

where $\phi = W_a - W_b + \hat{W}_a - \hat{W}_b$ represents the frequency change in the protected part of of the population, and incorporates the stabilizing contribution of protection from selection (this is where the stabilizing term fs_as_b appears in the simple protection from selection example Eq. (1)), and $\psi = W_a\hat{W}_a - W_b\hat{W}_b$ (cf. Eq. (7)).

It is not possible to completely disentangle the effects of protection from

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selection from density-regulated growth in Eq. (13), because both mechanisms rely on variation in T between iterations (that is, on competition between genotypes). If we had instead set up our serial transfer with a fixed growth time much smaller than the saturation time, then W_a and W_b are independent of genotype frequency and ϕ could not provide a rarity advantage. Thus, we cannot "switch off" density-regulated growth to examine protection from selection alone by fixing T in this manner. Instead, we evaluate how much protection extends the region of coexistence due to density-regulated growth alone.

Figure 3 shows the regions where $\psi > 0$, $\phi > 0$ and the protection-weighted combination of ϕ and ψ, Eq. (13), is positive. The $\phi > 0$ region includes the entire $\psi > 0$ region, indicating that protection extends the region of coexistence. The magnitude of this extension increases with $1/D$ because the stabilizing effect of protection depends on per-iteration selection coefficients, which in Yi and Dean's (2013) serial transfer model increase with the amount of growth $1/D$ between iterations (Sec. Density-regulated growth). In the limit of vanishingly small fluctuations ($D \to 1$), ϕ and ψ coincide.

It is well known that protection from selection is an effective stabilizer of coexistence (Chesson and Warner, 1981), and Fig. 3 reaffirms this. The more striking feature of Fig. 3 is just how effectively density-regulated growth alone is able to stabilize coexistence. The stabilization depends only on instantaneous growth rates, not on the overall magnitude of selection over an environmental iteration. Even if each growth cycle involves a 100-fold popula-

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tion expansion ($D = 0.01$), the region of coexistence due to density-regulated growth alone is of a similar size as the extended region when there is also fairly strong protection $f = 0.2$. For comparison, a 100-fold expansion means that even a relatively small difference in instantaneous growth rates will be amplified over $\log_2(1/D) \approx 7$ doublings to get substantial per-iteration selection coefficients, giving a strong stabilizing contribution from protection from selection (Sec. Protection from selection).

4 Discussion

It is perhaps not surprising that completely sheltering a substantial fraction of a population from competition has such a powerful effect. However, in many settings the amount of protection f is not expected to be particularly large. As we saw in Sec. Protection from selection, the fundamental time scale for evaluating protection from selection is the time scale of environmental variability. In many applications that have historically been of ecological interest, such as perennial plants subject to inter-annual variability in seed recruitment conditions, multiple environmental iterations occur over a generation. Protection in this context is closely connected to the presence of overlapping generations, and could be substantial on the timescale of a fraction of a generation. However, in species with a faster life cycle the opposite occurs: many generations pass within the timescale of appreciable environmental variation. For these species, the widespread association of protection from selection with overlapping generations (Ellner and Hairston,

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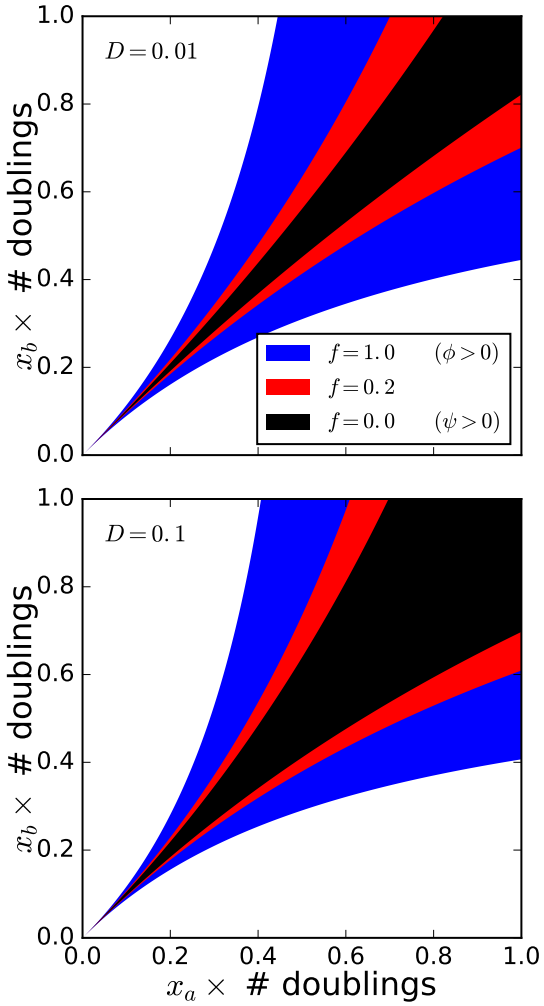

Figure 3: The region of coexistence stabilized by density-regulated growth alone (black region) is extended by protection from selection (red region) by an amount which depends on both the amount of protection f and the amount of growth which occurs as measured by the number of doublings measured by $\ln(1/D)$.

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1994; Svardal et al., 2015) is misleading. In the *Drosophila* example, the relevant timescale of environmental variation is seasonal, corresponding to multiple generations. The fact that *Drosophila* is iteroparous, with selection at the larval stage likely more intense than on adults, does not imply substantial protection over a season.

Coexistence stabilized by density-regulated growth could occur widely in species which experience "boom-bust" cycles, *Drosophila* being a notable example. Of course, the specifics for *Drosophila* are more complicated than the simple serial transfer example. Dilution is replaced with declining fruit availability and falling temperatures in the winter. Growth declines gradually rather than abruptly (see Supplement B for an analysis of the density-regulated growth mechanism with gradual resource depletion). Contests for fruit may become more intense as growth progresses. Nevertheless, *Drosophila* presumably experiences analogous indirect competition due to the limited time available before reaching high densities.

Diploidy with incomplete dominance is a strong form of protection at the allele level (Sec. Geometric mean heterozygote advantage). Since the underlying cause is heterozygozity and incomplete dominance, it is not sensitive to the timescale of environmental variability, unlike the case of overlapping generations.

The cyclical *Drosophila* polymorphisms identified by Bergland et al. (2014) are closely in phase with the seasons. Other mechanisms of coexistence with fluctuating allele frequencies, e.g. coevolution with parasites, are not expected to align so closely with the seasons. Recent genome-wide scans for all

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genes under balancing selection in *Drosophila* (not just those with cyclically varying allele frequencies) do identify innate immunity genes as among the top candidates Croze et al. (2017). In these important but less seasonally-aligned cases, coexistence would be driven by negative frequency dependence at the generational timescale due to the disadvantage of being the most abundant target for parasites (Fig. 2).

We can therefore make the following tentative predictions about the cyclical polymorphisms in Bergland et al. (2014). Density-regulated growth and incomplete dominance could plausibly be important stabilizers of polymorphism. By comparison, protection from selection as a result of overlapping generations is considerably weaker, and does not seem likely to be an important stabilizer. The role of parasites is more complicated, but if parasites are stabilizing the cyclical polymorphisms in Bergland et al. (2014), then it is not obvious why those cycles track the seasons so closely.

The serial transfer setup of Yi and Dean (2013) is unusual within the field of experimental evolution; normally, the same rather than fluctuating external environmental conditions are applied to each of the cycles, such that the only environmental fluctuations occur within rather than between cycles. As a result, the mechanisms underling coexistence in classical experimental evolution settings are quite different from those discussed here (Rozen and Lenski, 2000). However, it is worth emphasizing again that the presence of overlapping generations is not just unnecessary for protection from selection, it is also insufficient. In the case of Yi and Dean (2013), generations overlap to such an extent that the cells present at the start of a growth cycle and

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those produced by multiple rounds of reproduction are all present by the saturation phase. Yet protection from selection is only present if there is some shelter from competition for consumable resources over the course of a growth cycle.

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Supplement A: Coexistence criteria details

Here we give more detailed derivations of the coexistence conditions (2), (4), and (13).

Starting from Eq. (1), genotype a increases in frequency relative to genotype b over a complete environmental cycle of two environmental iterations if

$$\left(f + (1-f)\frac{w_a}{\overline{w}}\right)\left(f + (1-f)\frac{\hat{w}_a}{\hat{\overline{w}}}\right) > \left(f + (1-f)\frac{w_b}{\overline{w}}\right)\left(f + (1-f)\frac{\hat{w}_b}{\hat{\overline{w}}}\right), \tag{14}$$

where no hat denotes an iteration where a is favored, and a hat denotes an iteration where b is favored. For example, $w_a = 1 + s_a$ and $\hat{w}_a = 1$.

Multiplying out the terms in brackets on both sides, subtracting the right hand side, and dividing out the common factor $(1-f)$, we obtain

$$f\left(\frac{w_a}{\overline{w}} - \frac{w_b}{\overline{w}} + \frac{\hat{w}_a}{\hat{\overline{w}}} - \frac{\hat{w}_b}{\hat{\overline{w}}}\right) + (1-f)\left(\frac{w_a}{\overline{w}}\frac{\hat{w}_a}{\hat{\overline{w}}} - \frac{w_b}{\overline{w}}\frac{\hat{w}_b}{\hat{\overline{w}}}\right) > 0. \tag{15}$$

Assuming that a is rare, we have $\overline{w} = 1$ and $\hat{\overline{w}} = 1 + s_b$, and Eq. (15) becomes

$$f\left(s_a - \frac{s_b}{1+s_b}\right) + (1-f)\left(\frac{s_a - s_b}{1+s_b}\right) > 0 \tag{16}$$

The term in brackets on the left can be written as $(s_a - s_b + s_a s_b)/(1+s_b)$. Multiplying by $1 + s_b$ and rearranging, we obtain Eq. (2).

Turning to Eq. (3), the analogue of (14) for coexistence in the diploid

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case is

$$\left(f\frac{w_{ab}}{\overline{w}}+(1-f)\frac{w_{aa}}{\overline{w}}\right)\left(f\frac{\hat{w}_{ab}}{\hat{\overline{w}}}+(1-f)\frac{\hat{w}_{aa}}{\hat{\overline{w}}}\right)>$$
$$\left((1-f)\frac{w_{ab}}{\overline{w}}+f\frac{w_{bb}}{\overline{w}}\right)\left((1-f)\frac{\hat{w}_{ab}}{\hat{\overline{w}}}+f\frac{\hat{w}_{bb}}{\hat{\overline{w}}}\right), \tag{17}$$

where $f=1-p_a=p_b$. Assuming that a is rare, all terms multiplied by $1-f$ are negligible, and Eq. (17) becomes

$$w_{ab}\hat{w}_{ab}>w_{bb}\hat{w}_{bb}. \tag{18}$$

Substituting the fitnesses $w_{ab}=1+\frac{s_b}{2}$, $\hat{w}_{ab}=1+\frac{s_a}{2}$, $w_{bb}=1$ and $\hat{w}_{bb}=1+s_b$, we obtain Eq. (4). Note that in Sec. Geometric mean heterozygote advantage we tacitly assumed that the environment changes every generation, since Eq. (3) governs allele frequency change over a single round of random mating. Allowing multiple generations per environmental iteration would not substantively alter the finding of a strong stabilizing effect, since the underlying cause is the protection of almost all rare type alleles in heterozygotes, which is independent of environmental time scale.

To obtain Eq. (13), note that Eq. (12) is the same as Eq. (1) with $w_a/\overline{w}$ substituted for W_a (and similarly for the other fitnesses), except that it governs abundances instead of frequencies. The switch to abundances makes no difference, and Eq. (14) determines when a increases in frequency relative to b after this substitution of fitnesses. Eq. (13) is just Eq. (15) after this substitution.

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Supplement B: Density-regulated growth with explicit resource consumption

Here we generalize the exponential growth model of Yi and Dean (2013) to explicitly represent resource consumption. We show that coexistence due to density-regulated growth is not sensitive to their model of exponential growth up to sudden saturation. Moreover, we show that growth need not have saturated at all for coexistence to occur, although saturation can expand the region of coexistence considerably.

We assume that there is a single limiting resource $L(t)$ which is replenished to the same level $L_0 = L(0)$ at the beginning of each iteration but is not replenished while growth occurs. Here t denotes time from the start of a given growth cycle. Resources are consumed linearly such that

$$\frac{dn_a}{dt} = yu_a L n_a, \tag{19}$$

and similarly for the b type, where u_a is the resource uptake rate and y is the yield factor per unit of L. For simplicity, we have assumed that the yield factors are equal $y = y_a = y_b$ for both types. We have also assumed negligible mortality over a growth cycle. These assumptions merely keep our equations a bit neater, the analysis of this section is not substantively modified by different yields, or the inclusion of mortality or metabolic upkeep such as in Li and Chesson (2016).

The resource L is consumed at rate

$$\frac{dL}{dt} = -\overline{u} N L, \tag{20}$$

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where $\overline{u} = (u_a n_a + u_b n_b)/N$. Since the yields are identical, the total amount of the limiting resource (both consumed and unconsumed) remains constant over a growth cycle, and is given by

$$K_L = \frac{N}{y} + L. \tag{21}$$

(The constancy of K_L can be verified by substituting Eqs. (19) and (20) into the time derivative of Eq. (21)).

As in Sec. Density-regulated growth, the a type is assumed to be rare ($n_a \ll n_b \approx N$). This implies that $\overline{u} \approx u_j$ remains approximately constant over a growth cycle. Thus, combining Eqs. (20) and (21), we see that resource depletion is logistic

$$\frac{dL}{dt} = -\overline{g}\left(1 - \frac{L}{K_L}\right) L, \tag{22}$$

$$L(t) = \frac{L_0 K_L}{L_0 + (K_L - L_0)e^{\overline{g}t}}, \tag{23}$$

where, by analogy with Sec. Density-regulated growth, we introduce the notation $g_a = y u_a K_L$ for the maximal possible exponential growth rate that would be obtained if all resources were unconsumed ($L = K_L$), and $\overline{g} = y\overline{u}K_L$. Similarly, the overall abundance grows logistically

$$N(t) = \frac{N_0 K}{N_0 + (K - N_0)e^{-\overline{g}t}} \tag{24}$$

where N_0 is the total abundance at $t = 0$, and $K = yK_L$ is the carrying capacity.

It is then straightforward to solve Eq. (19) by integrating $L(t)$,

$$F(t) = \int_0^t L(\tau)d\tau = K_L\left[t + \frac{\ln(L(t)/L_0)}{\overline{g}}\right], \tag{25}$$

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since then we have

$$\frac{dn_a}{dt} = yu_a \frac{dF}{dt} n_a, \tag{26}$$

and so

$$\begin{aligned} n_a(t) &= n_i(0) e^{yu_a F}, \\ &= n_a(0) e^{g_a t} \left(\frac{L(t)}{L_0} \right)^{g_a/\overline{g}}, \\ &= n_a(0) \left(\frac{e^{\overline{g}t} L(t)}{L_0} \right)^{g_a/\overline{g}}, \\ &= n_a(0) \left(\frac{N(t)}{N_0} \right)^{g_a/\overline{g}}. \end{aligned} \tag{27}$$

Finally, incorporating dilution between iterations, and denoting the constant duration of each cycle by T_E, we arrive at the analogue of Eq. (6)

$$n'_a = DG^{g_a/\overline{g}} n_a, \tag{28}$$

and similarly for b, where $G = N(T_E)/N_0$ is the overall growth factor over the cycle. The difference in log growth rates over a cycle is then given by

$$r_a - r_b = \left(\frac{g_a}{g_b} - 1 \right) \ln G, \tag{29}$$

and so

$$\begin{aligned} \langle r_a - r_b \rangle &= \frac{1}{2} \left(\frac{g_a}{g_b} - 1 \right) \ln G + \frac{1}{2} \left(\frac{\hat{g}_a}{\hat{g}_b} - 1 \right) \ln \hat{G}, \\ &= \frac{1}{2} \left(x_a \ln G - \frac{x_b}{1 + x_b} \ln \hat{G} \right) \\ &= \frac{1}{2} \frac{\ln G}{1 + x_b} \left(x_a + x_a x_b - \alpha x_b \right), \end{aligned} \tag{30}$$

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where $\alpha = \ln \hat{G} / \ln G$ is the ratio of the overall number of doublings when b is favored to when it is not. This is positive if and only if Eq. (9) holds. In the particular case that T_E is sufficiently large that growth saturates each cycle $N(T_E) \approx K$, then $\alpha = 1$ and Eq. (9) simplifies to Eq. (8).