Research article

Partial protection from fluctuating selection can lead to evolution towards amplified fluctuation in population size

Yuseob Kim

Division of EcoScience and Department of Life Science, Ewha Womans University

Ewhayeodae-gil 52, Seodaemun-gu, Seoul, Korea 03760

yuseob@ewha.ac.kr

Keywords: fluctuating selection, storage effect, absolute fitness, population size, Parrondo's paradox

Abstract

Cyclic or random fluctuation of selective environment is prevalent in nature. A simple mathematical model for coupled demographic and evolutionary dynamics under such an environment was investigated. In a population that is made of a subpopulation subject to temporally fluctuating selection and another subpopulation protected from such selection, negative frequency-dependent selection leading to the stable maintenance of polymorphism, termed the storage effect, is known to emerge. However, when the model was reformulated based upon the absolute fitness, negative frequency-dependency was found to be restricted to a constant-sized population under strong density regulation. Under weaker density regulation, an allele that causes the wider fluctuation of absolute fitness in the first subpopulation was found to be positively selected and driven to fixation, even if this allele is not favored in either subpopulation in isolation. This positive selection requires simply that the allele is randomly moving between subpopulations. Selection for alleles causing wider fitness fluctuation means that evolution occurs toward wider fluctuation of population size, whereas a classical theory suggested the opposite. In addition, pre-existing oscillation in population size selects for a variant whose relative fitness varies in phase with population size changes, even when this variant has no selective advantage over the other allele in relative fitness. Fixation of such a variant can further increase the amplitude of population size fluctuation. The discovery of these novel forms of natural selection highlights the complexity and diversity of two-way interactions between demographic and evolutionary genetic processes.

Significance statement

Natural populations undergo demographic (e.g. population size) and evolutionary genetic changes. Both are greatly affected by the cyclic or random fluctuation of environment. In this study, the joint dynamics of demographic and evolutionary changes are investigated using a mathematical model in which one part of a population is under fluctuating selective environment and the other part is protected from such selection. Under such a condition, variants causing wider fluctuation in reproductive output, thus greater oscillation in population size, were found to be positively selected. Classical theory however suggested that evolution should occur toward smaller fluctuation in population size. This study therefore revealed an unexpected form of natural selection, stemming from complex interaction between ecological and evolutionary dynamics.

Introduction

Natural populations face cyclic or random fluctuation of abiotic and biotic environment that leads to fluctuation in individuals' fitness (GRANT AND GRANT 2002; BELL 2010; THOMPSON 2013). Evolution under fluctuating selection has been a major topic in population genetics. Theoretical models were explored to investigate the effect of fluctuating selection on various aspects of evolution such as the level of both neutral and non-neutral genetic variation (DEMPSTER 1955; HALDANE AND JAYAKAR 1963; HEDRICK 1976; HEDRICK 1986; GILLESPIE 1994; BARTON 2000; HUERTA-SANCHEZ *et al.* 2008). Recently balancing selection under seasonal fluctuation of fitness has received particular attention as a potential explanation for the apparent seasonal oscillation of allele frequencies at thousands of nucleotide sites in temperate *Drosophila melanogaster* populations (BERGLAND *et al.* 2014; WITTMANN *et al.* 2017; MACHADO *et al.* 2021). One area of theoretical development focused on the effect of protecting a subset of population or particular stage in life cycle from fluctuating selection in increasing the species or allelic diversity (CHESSON AND WARNER 1981; ELLNER AND HAIRSTON 1994; GULISIJA AND KIM 2015; SVARDAL *et al.* 2015; BERTRAM AND MASEL 2019), which is commonly called the storage effect. This effect occurs as negative frequency-dependent selection emerges in the presence of refuge from selection, such as seed bank (TURELLI *et al.* 2001), even though in each subpopulation fitness is not given as the function of allele frequency. It can generate stable long-term polymorphism at multiple loci (PARK AND KIM 2019), although it requires strong selection (a large magnitude of fitness oscillation; BERTRAM AND MASEL (2019)).

Partial protection to fluctuating selection, leading to the storage effect, is expected not only with seed bank but also under other commonly encountered conditions in plants and animals. The survival of individuals in diapause, for example in the pupal stage of insects, are probably unaffected by variable environment (HEDRICK 1995). In species with overlapping generations, only a portion of a population will be subject to selection on a trait that is expressed at a particular stage of life-cycle (CHESSON AND WARNER 1981; ELLNER AND HAIRSTON 1994). In dioecious species, alleles affecting female reproductive traits, for example, are protected from selection if they are carried by males (REINHOLD 2000). If an allele conferring genetic robustness or phenotypic plasticity is segregating in a population, it constitutes a genetic background on which new mutants are protected from selection (GULISIJA *et al.* 2016). In all of these cases, a species effectively consists of a subpopulation exposed to selection and another subpopulation, the refuge, protected from selection, between which individuals (*i.e.* alleles) move with certain probability per unit time.

Without strict density regulation, fitness fluctuation will translate into the fluctuation of population

size. Despite this, theoretical models for the storage effect have considered an infinitely large or constant-sized populations, under which the evolutionary dynamics is fully described by the relative fitness and the relative frequencies of alleles. In this study, the storage effect was modeled with absolute fitness, which allowed joint changes in demography (population size) and allele frequencies. The following considerations motivated this exploration. First, the outcome of natural selection under changing population size can be different from that under constant population size, as shown in the case of the fixation probability of beneficial alleles (OTTO AND WHITLOCK 1997) or the nature of fitness that is maximized (SÆTHER AND ENGEN 2015). In this study, whether the storage effect under variable population sizes under relaxed density regulation can still generate negative frequency-dependent selection is of particular interest. Second, conversely, certain demographic changes may occur as the results of natural selection, as in the case of evolutionary rescue/trapping (CARLSON *et al.* 2014). This study is concerned about the effect of fluctuating selection in the presence of refuge on the fluctuation of population size. It is ultimately anticipated that, as numerous studies using simple mathematical models demonstrated (PIMENTEL 1961; CHARLESWORTH 1971; ROUGHGARDEN 1971; LION 2018), two-way interaction arises between demographic and evolutionary dynamics, which is generally described as an eco-evolutionary feedback (reviewed in GOVAERT *et al.* (2019)).

Assuming that there are two alleles whose absolute fitness fluctuate differently but yield the same geometric mean fitness outside the refuge, I found that an allele with wider fluctuation in absolute fitness is positively selected under weak or moderate regulation of population density. Namely, directional, not negative frequency-dependent, selection occurred and resulted in the amplification of population size fluctuation. More surprisingly, pre-existing oscillation in population size was found to generate positive selection for an allele whose relative fitness oscillates in phase with population size oscillation, although it is quasi-neutral or even deleterious outside the refuge. This study therefore provides a novel example of eco-evolutionary feedback and demonstrates the importance of modelling based on absolute fitness. At the end, it will be discussed how the finding in this study is related to the evolution of bet-hedging (SEGER AND BROCKMANN 1987; PHILIPPI AND SEGER 1989) and to Parrondo's paradox, a counter-intuitive finding in game theory that two losing games can combine to generate a winning game (HARMER AND ABBOTT 2002), which is analogous to the current result of one allele positively growing in numbers simply by moving between two subpopulations while no growth is expected within either subpopulation.

Storage effect under the fluctuation of relative fitness

I briefly review the theory of the storage effect (CHESSON AND WARNER 1981; GULISIJA AND KIM 2015; BERTRAM AND MASEL 2019). Consider a population of haploid individuals that carry either A_1 or A_2 alleles with relative frequencies p and q. (Note that this model can be directly translated into that of two species competing for common resources.) Reproduction occurs in discrete generations. Here a large and constant population size is implicitly assumed, the effect of which will be addressed later. Trade-off in allelic fitness over different environments (different phases in an environmental cycle) is assumed: the relative fitness of A_1 to A_2 are given by $w_1 = e^{s_t}$ and $w_2 = 1$ under strict density regulation, where

$$s_t = s_{max} \sin\left[\frac{2\pi t}{\lambda}\right]. \tag{1}$$

Namely, over a cyclically (e.g. seasonally) changing environment with the period of λ generations, there is no net advantage or disadvantage between alleles. Allele frequencies are not expected to change in this population: with p' and q' the frequencies after a single cycle,

$$\frac{p'}{q'} = \left(\prod_{t=1}^{\lambda} \frac{w_1}{w_2}\right)\frac{p}{q} = \exp\left[\sum_{t=1}^{\lambda} s_t\right]\frac{p}{q} = \frac{p}{q}.$$

Now, it is assumed that this population is divided in fraction 1-r and r and only the first subpopulation resides in an environment subject to the above fluctuating selection, which I simply call the "field". In the second subpopulation, individuals have identical fitness regardless of alleles thus being protected from fluctuating selection. While this "refuge" from selection primarily models a seed bank, it may also correspond to a certain stage of life cycle in species with overlapping generations, a spatially separated population with relaxed selection, or a particular sex that is not the target of sex-limited selection. (Many of these are true for diploid species but the current haploid model should be applicable to diploids with incomplete dominance.) We also assume that individuals are redistributed into the field and the refuge, with probability 1-r and r respectively, during the migration step of each generation. Let p_t be the frequency of A_1 at generation t. It is assumed that A_1 recently arose by mutation and therefore p_t is close to 0. Then, after one cycle of fluctuating selection, frequency $p_{t+\lambda}$ is expected to be larger than p_t because

$$p_{t+\lambda} = p_t \prod_{i=1}^{\lambda}\left((1-r)\frac{w_1}{\bar{w}} + r\right)$$

$$\approx p_t \prod_{i=1}^{\lambda} \left((1-r)\frac{w_1}{w_2} + r \right) = p_t \exp\left[\sum_{i=1}^{\lambda} \log[\,(1-r)\frac{w_1}{w_2} + r] \right]$$

$$\geq p_t \exp\left[\sum_{i=1}^{\lambda} \left((1-r)\log\frac{w_1}{w_2} + r\log 1 \right) \right] = p_t \left(\prod_{i=1}^{\lambda} \frac{w_1}{w_2} \right)^{1-r} = p_t. \quad (2)$$

The mean fitness on the field $\bar{w} = pw_1 + qw_2$ is approximated by w_2 with $p \ll q$ and Jensen's inequality was applied above. No change in allele frequency ($p_{t+\lambda} = p_t$) occurs only if fluctuating selection is turned off ($s_{max} = 0$). Therefore, the presence of refuge confers an advantage to a rare allele under fluctuating selection, thus the storage effect.

Furthermore, the above analysis suggests that, to generate the storage effect, the change of environment on the field (fluctuation of w_1 versus w_2) does not have to be periodic as long as the product of $\frac{w_1}{w_2}$ over successive generations converges to 1. To confirm this, the iteration of allele frequencies according to the model above was made using $s_t = s_{max}\sin[2\pi t^*/\lambda]$, where t^* is a random integer between 1 and λ drawn each generation. Interestingly, the rare allele increased in frequency slightly faster on average under this mode of random fluctuating selection than under the periodic ("unscrambled") fluctuation (Fig. 1).

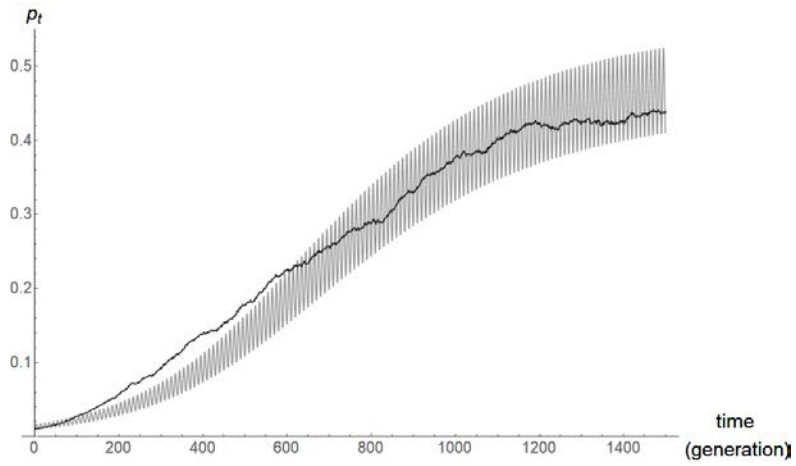

Figure 1. Frequency of A_1 allele (p_t) over time t (in generations) under periodic (gray curve; using $s_t = s_{max}\sin(2\pi t/\lambda)$) or random (dark curve; using $s_t = s_{max}\sin[2\pi t^*/\lambda]$, averaged over 300 replicates) fluctuation of fitness in a population subdivided into the field and the refuge, under the relative fitness-based model. Other

The storage effect is very intriguing because a rare allele is positively selected simply by randomly moving between field and refuge, while it is not favored in either subpopulation. It is even possible that a slightly deleterious allele (i.e. having a smaller geometric mean fitness than the other on the field) is positively selected

when it is rare (GULISIJA AND KIM 2015). A plain explanation for this phenomenon was that the loss of an allele from the field during an unfavorable period is buffered by its presence in the refuge and then, during the next period when the same allele is now favored on the field, the refuge supplies the copies of this allele into the field. However, the buffering effect of refuge should apply to the other (common) allele too. It is therefore not easy to explain (verbally) why a negative frequency-dependency arises in this model. GULISIJA AND KIM (2015) pointed out that difference between rare and common alleles lies in the relative magnitude of allele frequency fluctuation: on the field the frequency of the rare allele (A_1 in this example) fluctuates in greater proportion, as $w_1/\overline{w} \approx w_1/w_2$ oscillates heavily, than the common allele ($w_2/\overline{w} \approx 1$). Note that, under a strict density regulation, $w_1/\overline{w}$ and $w_2/\overline{w}$ are the absolute fitness (per-capita number of progenies) of these two types of individuals. It is clear from the above analysis (eq. 2), where Jensen's inequality arises, that an allele that is positively selected is the one with larger fluctuation in absolute fitness.

Cyclic fluctuation of absolute fitness: constant carrying capacity

The above model based on the relative fitness and relative frequencies of the alleles does not assume any particular population dynamics regarding the absolute population size. However, fluctuating environment is likely to generate fluctuation in population size if population density is not strictly regulated. The dynamics of allele frequency changes may depend on whether population size vary in time or not. I therefore expanded the above model to allow the sizes of subpopulations to change according to the absolute fitness of individuals under varying degrees of population density regulation.

Let n_{1f} and n_{2f} (n_{1r} and n_{2r}) be the numbers of A_1 and A_2 individuals on the field (in the refuge). In the absence of density regulation, n_{1f} and n_{2f} are assumed to increase to $W_{1f}n_{1f}$ and $W_{2f}n_{2f}$ over a generation in the field. Namely, W_{1f} and W_{2f} are the absolute fitness of A_1 and A_2, which may change over time. Absolute fitness for both alleles in the refuge is given by W_r. For density regulation, I define the carrying capacities of the field and refuge to be K_f and K_r, which may also change over time. In addition, it is assumed that, after steps of growth and density regulation, individuals in the field migrate to the refuge with probability m_{fr} and those in the refuge migrate to the field with probability m_{rf}. Then, the numbers of A_1 and A_2 individuals in the field and refuge in the next generation become

$$n'_{1f} = (1 - m_{fr})W_{1f}n_{1f}R\left[W_{1f}n_{1f} + W_{2f}n_{2f}, g_f, K_f\right] + m_{rf}W_r n_{1r}R[W_r(n_{1r} + n_{2r}), g_r, K_r], \quad (3a)$$

$$n'_{2f} = (1 - m_{fr})W_{2f}n_{2f}R\left[W_{1f}n_{1f} + W_{2f}n_{2f}, g_f, K_f\right] + m_{rf}W_r n_{2r}R[W_r(n_{1r} + n_{2r}), g_r, K_r], \quad (3b)$$

$$n'_{1r} = m_{fr}W_{1f}n_{1f}R\left[W_{1f}n_{1f} + W_{2f}n_{2f}, g_f, K_f\right] + \left(1 - m_{rf}\right)W_r n_{1r}R[W_r(n_{1r} + n_{2r}), g_r, K_r], \quad (3c)$$

and

$$n'_{2r} = m_{fr}W_{2f}n_{2f}R\left[W_{1f}n_{1f} + W_{2f}n_{2f}, g_f, K_f\right] + \left(1 - m_{rf}\right)W_r n_{1r}R[W_r(n_{1r} + n_{2r}), g_r, K_r], \quad (3d)$$

where

$$R[N, g, K] = \frac{1+g}{1+g\frac{N}{K}} \quad (3e)$$

determines the strength of density regulation: if individuals carry only neutral alleles and the population size N is much smaller than its carrying capacity K, population will grow at rate g. Therefore, a large value of g (≥ 0) means strong density regulation and the relative fitness-based model above is restored with $g \to \infty$. Different strengths of regulation, g_f and g_r, can be applied to the field and the refuge.

First, how population evolves under this absolute fitness-based model was explored numerically by the recursion of eq. (3). Constant carrying capacity for the field ($K_f = 1000$) and immediate redistribution over subpopulations ($m_{fr} = m_{rf} = 0.5$) were initially assumed. Four values of g_f that represent the increasing strength of density regulation on the field were used (0.02, 0.2, 2, and 20). For the refuge, $g_r = 0$ is assumed (as the model of seed bank is primarily considered). Then, the fitness of A_1 and A_2 was given by $W_{1f} = e^{0.5s_t}$, $W_{2f} = e^{-0.5s_t}$, and $W_r = 1$, where s_t is given by eq. (1). Namely, the oscillation in absolute fitness of the two alleles is symmetric on the field. Starting from a low frequency (0.01), A_1 allele increased toward frequency 0.5 and this change happened faster with larger g (Figure 2A), consistent with the result from the relative fitness-based model.

Now the fitness scheme is changed to $W_{1f} = e^{s_t}$ and $W_{2f} = 1$, which keeps the relative fitness identical to the above but lets the absolute fitness of A_1 fluctuate more than that of A_2. This dramatically changed the course of evolution (Figure 2B). With strong density regulation (g = 20), the frequency of A_1 approached close to 0.5, as before. However, under weaker density regulation, the absolute count of A_1 continued to increase toward $2K_f$, while that of A_2 decreased toward zero. Similar results are obtained when the absolute fitness of both alleles fluctuate but the fluctuation of A_1 is larger (e.g. $W_{1f} = e^{1.5s_t}$ and $W_{2f} = e^{0.5s_t}$). Namely, an allele

increases in frequency by directional, not negative frequency-dependent, selection if its absolute fitness fluctuates more than the other allele. Switching the fitness oscillation of A_1 and A_2 ($W_{1f} = 1$ and $W_{2f} = e^{-st}$) confirmed this conclusion (Figure 2C). Consequently, unless density regulation is strong, population evolves towards having greater fluctuation in size.

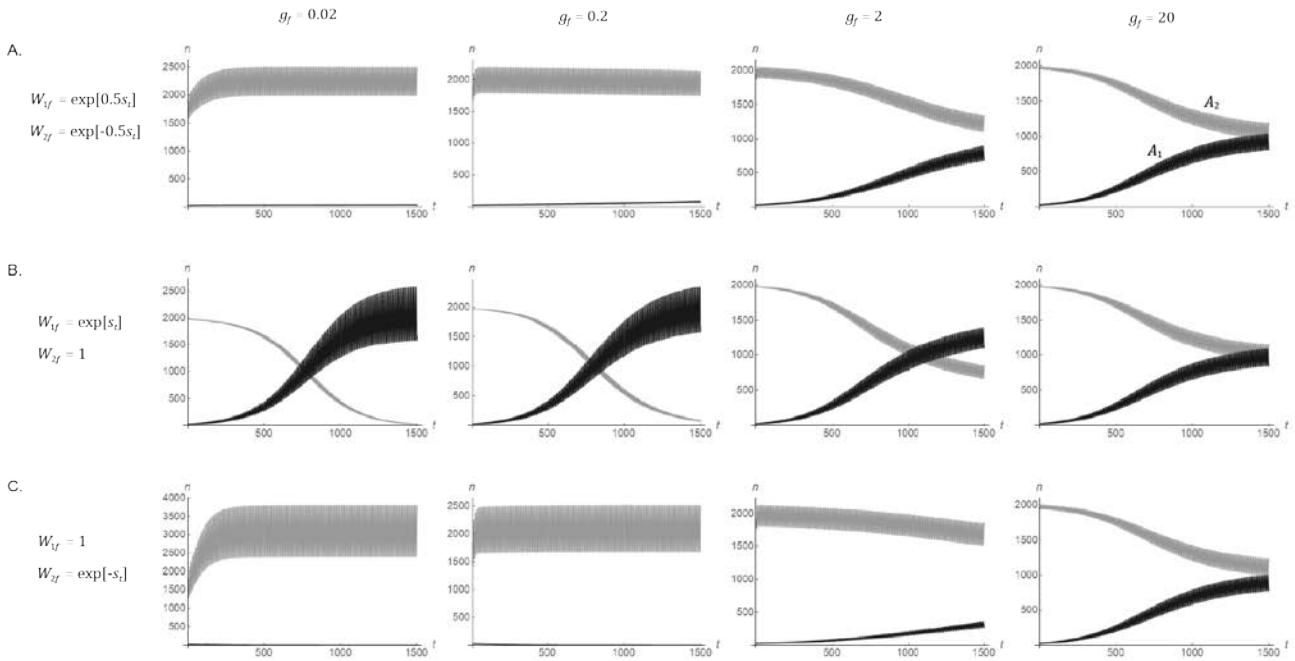

Figure 2. Changes in the absolute frequencies of A_1 ($n_1 = n_{1f} + n_{1r}$; dark curves) and A_2 alleles ($n_2 = n_{2f} + n_{2r}$; gray curves) in a population subdivided into the field and the refuge ($m_{fr} = m_{rf} = 0.5$), according to deterministic recursion of eq. (3) starting from $n_{1f} = n_{1r} = 10$ and $n_{2f} = n_{2r} = 990$. Note that, as these graphs are unable to resolve curves oscillating very rapidly on the scale of time (in generations) shown above, they appear in the shape of bands. The field maintains a constant carrying capacity ($K_f = 1{,}000$) with varying strengths (g_f) of density regulation. Other parameters: $W_r = 1$, $g_r = 0$, $s_{max} = 0.3$, $\lambda = 10$.

This result can be understood using a simple analysis at the limit of no density regulation ($g_f = 0$). In this case, the number, n, of haploid individuals carrying a given allele changes independently of the other allele. Assuming that $m_{fr} = r$ and $m_{rf} = 1 - r$ and that this allele has the absolute fitness of W_f and W_r on the field and in the refuge, n changes to $n((1-r)W_f + rW_r)$ over a generation. Starting from n_0 the number of individuals after a single cycle of fitness fluctuation is given by

$$n_\lambda = n_0 \prod_{t=1}^{\lambda}\left((1-r)W_f + rW_r\right) = n_0 \exp\left(\sum_{t=1}^{\lambda} \log\left[(1-r)W_f + rW_r\right]\right) \quad (4)$$

Since log x is a concave function of x, as long as $W_f \neq W_r$, $\log\left[(1-r)W_{f,t} + rW_r\right]$ is always greater than $(1-$

$r)\log[W_{f,t}] + r\log[W_r]$ and this difference increases as $W_{f,t}$ deviates further from W_r. If temporal fitness fluctuation on the field is given by $W_f = \exp\left[\alpha \sin\left(\frac{2\pi t}{\lambda}\right)\right]$, where α determines the amplitude of fluctuation that may also incorporate the effect of an ecological factor that will be considered later, with $W_r = 1$

$$\log[(1-r)W_{f,t} + rW_r] = \log\left[(1-r)\exp\left[\alpha \sin\left[\frac{2\pi t}{\lambda}\right]\right] + r\right] \approx \alpha(1-r)\sin\left[\frac{2\pi t}{\lambda}\right] + \frac{\alpha^2 r(1-r)}{4}\left(1 - \cos\left[\frac{4\pi t}{\lambda}\right]\right)$$

after Taylor expansion around α = 0 up to second order. Therefore,

$$n_\lambda \approx n_0 \exp\left[\frac{1}{4}\alpha^2 r(1-r)\lambda\right] \approx n_0\left(1 + \frac{1}{4}\alpha^2 r(1-r)\lambda\right) \quad (5)$$

Namely, the absolute number of individuals increases as long as their absolute fitness fluctuates on the field, when no such change is expected on the field or refuge in isolation ($\prod_t W_f = 1$ and $W_r = 1$). However, the rate of this increase is smaller than the order of α^2: a significant change is expected only if the amplitude of fluctuation is large.

Now, the result shown in Figure 2 can be understood in terms of eq. (5). In case of individuals carrying A_1 allele with absolute fitness $W_{1f} = e^{st}$, the size of A_1 subpopulation increases exponentially under $g_f = 0$ (*i.e.* if T is a multiple of λ, $n_{1,T} \approx n_0 \exp\left[\frac{1}{4}{s_{max}}^2 r(1-r)T\right]$, which agrees very well with the exact recursion; Figure S1). With positive (albeit weak) density regulation ($g_f > 0$), the number of A_1 cannot increase indefinitely. However, A_1 outcompetes A_2 whose absolute fitness fluctuates less ($W_{2f} = 1$ in Figure 2B). Namely, two alleles change in numbers according to the intrinsic growth rates given by eq. (5) (thus eq. 4) before density regulation is applied and their ratio determines the change of their relative frequencies. Under strong density regulation ($g_f \gg 1$), the relative frequency of A_1 approaches to a stable fluctuation around 0.5, at which n_1 and n_2 must fluctuate symmetrically so that their intrinsic rates of growth suggested by eq. (5) becomes equal.

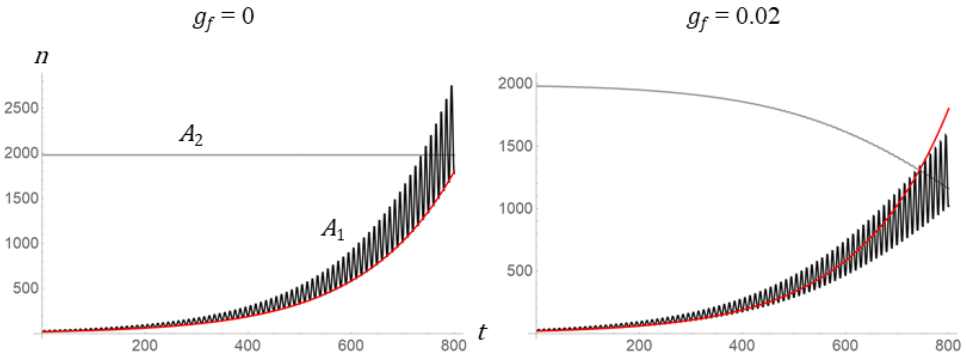

Figure S1. Comparison between the changes of n_1 according to exact recursion (eq. 3; dark curves) and approximation by $n_0 \exp\left[\frac{s_{max}^2}{16} t\right]$ (red curves) in populations with $m_{fr} = m_{rf} = 0.5$ under weak density regulation (g_f = 0 or 0.02). Fitness is given by $W_{1f} = \exp(s_t)$ and $W_{2f} = 1$, with s_{max} = 0.3. The changes of n_2 by eq. (3) is shown in gray curves.

Cyclic fluctuation of absolute fitness: oscillating carrying capacity

Next, the carrying capacity of the field was set to change cyclically, again with period λ: $K_f = K_{f0} \exp\left[\beta \sin\left[\frac{2\pi t}{\lambda}\right]\right]$, assuming β >0 without the loss of generality. This models population cycles in many species, which is commonly found to be symmetric oscillations in the logarithmic scale (MYERS 1988). Then, the fitness scheme of $W_{1f} = e^{0.5 s_t}$ and $W_{2f} = e^{-0.5 s_t}$, for example, means that A_1 (A_2) allele acts to amplify (dampen) the oscillation of population size beyond the level specified by the ecological factor β. The recursion of eq. (3) under this parameter set revealed that A_1 allele is positively selected to reach fixation, surprisingly, even under strong density regulation (g_f = 20) (Figure 3A). Similar rates of increase in n_1 over n_2 under $g_f > 1$ were observed with other fitness schemes: $(W_{1f}, W_{2f}) = (e^{s_t}, 1)$ or $(1, e^{-s_t})$ (Figures 3B,C). Therefore, under strong density regulation an allele is positively selected if its fluctuation in relative fitness is in phase with population size (carrying capacity) fluctuation. With weak density regulation ($g_f = 0.02$), it is an allele with larger amplitude in absolute fitness fluctuation that outcompetes the other, as in the case of constant carrying capacity (Figures 2B and 3B). Whenever A_1 outcompetes A_2 under weak or moderate density regulation ($g_f \leq 2$), the fluctuation of population size is wider than before (Figure 3).

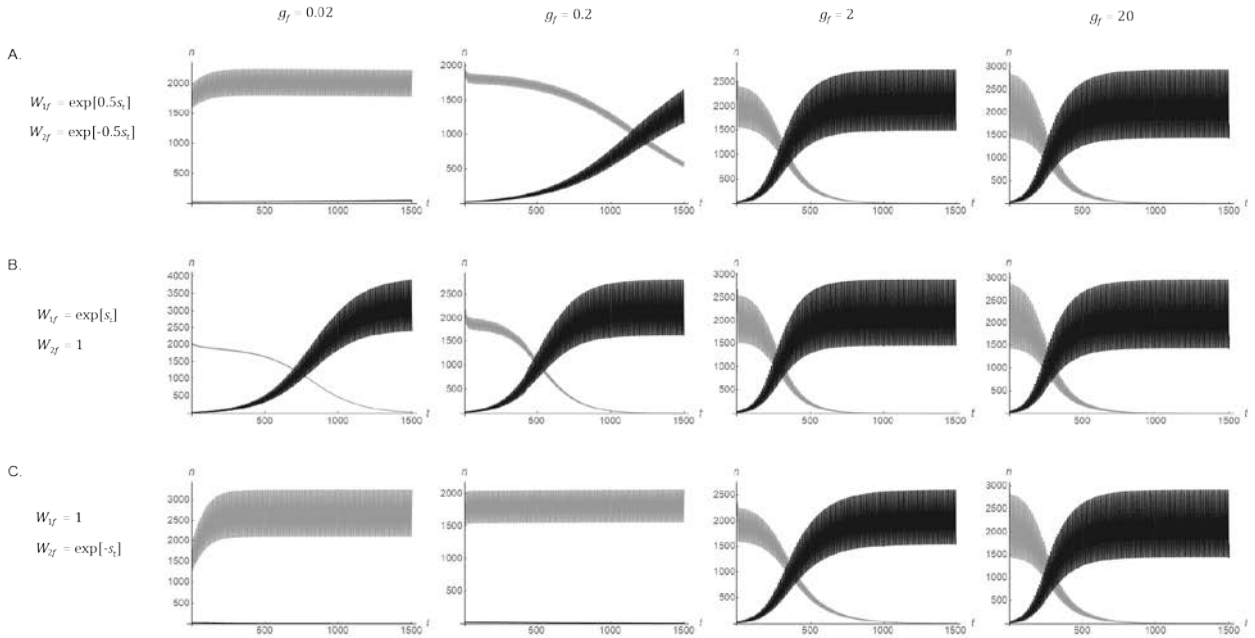

Figure 3. Changes in the absolute frequencies (n_1 and n_2) of A_1 (dark curves) and A_2 (gray curves) alleles under the cyclic fluctuation of carrying capacity on the field ($K_{f0} = 1{,}000$ and β = 0.5). Other parameters are identical to those in Figure 2.

To understand the above result for $g_f \gg 1$, a simpler model at the limit of strong density regulation is analyzed assuming a cyclic environment with λ = 2 in which each period is made of one "summer" and one "winter" generation. The carrying capacity of the field then alternates between K_S and K_W, where $K_\mathrm{S} \geq K_\mathrm{W}$. The absolute fitness of A_1 and A_2 individuals on the field are assumed to be W_1 and W_2 in summer and W_1^{-1} and W_2^{-1} in winter. In the refuge, $W_r = 1$. Under the assumption of $m_{fr} = m_{rf} = 0.5$ again and strict density regulation on the field but no density regulation in the refuge ($g_f \to \infty$ and $g_r = 0$), this population reaches a demographic equilibrium in which the total size alternates between N_S (at the end of summer generation) and N_W (at the end of winter generation). Because there are K_S individuals on the field and $N_\mathrm{W}/2$ in the refuge at the end of summer, $N_\mathrm{S} = K_\mathrm{S} + N_\mathrm{W}/2$ and, similarly, $N_\mathrm{W} = K_\mathrm{W} + N_\mathrm{S}/2$. Therefore, $N_\mathrm{S} = (4K_\mathrm{S} + 2K_\mathrm{W})/3$ and $N_\mathrm{W} = (2K_S + 4K_W)/3$. Let n_1 and n_2 be the number of A_1 and A_2 individuals at the end of winter (therefore, $n_1 + n_2 = N_\mathrm{W}$). Then, n_1 increases to

$$n'_1 = \frac{1}{2} n_1 W_1 \frac{K_\mathrm{S}}{\frac{1}{2} n_1 W_1 + \frac{1}{2} n_2 W_2} + \frac{1}{2} n_1 W_r = n_1 \left(\frac{K_\mathrm{S}}{n_1 + n_2/\omega} + \frac{1}{2} \right) = n_1 \left(\frac{2K_\mathrm{S}}{N_\mathrm{W}} \frac{1}{p + (1-p)/\omega} + \frac{1}{2} \right) \quad (6)$$

at the end of summer generation, where $\omega = W_1/W_2$ is the relative fitness of A_1 on the field in summer and $p = n_1/(n_1 + n_2)$. Eq. (6) shows that, as expected under strict density regulation, the evolutionary change of n_1

is dependent on the relative, not absolute, fitness of alleles. However, it is also dependent on the change of population size on the field (from $0.5N_{\mathrm{W}}$ to K_{S}), because the absolute, not relative, frequency of alleles is being tracked here. Similarly, at the end of the following winter generation, the number of A_1 individuals changes to

$$n''_1 = n'_1\left(\frac{K_{\mathrm{W}}}{n'_1 + n'_2\omega} + \frac{1}{2}\right) = n'_1\left(\frac{2K_{\mathrm{W}}\left(n_1 + n_2\frac{1}{\omega}\right)}{2K_{\mathrm{S}}(n_1+n_2) + n_1^2 + n_2^2 + n_1n_2\left(\omega + \frac{1}{\omega}\right)} + \frac{1}{2}\right)$$

$$= n'_1\left(\frac{\frac{2K_{\mathrm{W}}}{N_{\mathrm{W}}}\left(p+(1-p)\frac{1}{\omega}\right)}{\frac{2K_{\mathrm{S}}}{N_{\mathrm{W}}}+1+p(1-p)\left(\omega+\frac{1}{\omega}-2\right)} + \frac{1}{2}\right) \tag{7}$$

When A_1 is rare ($p \to 0$) the change of its absolute frequency after a cycle as a function of ω is described by

$$f(\omega) \equiv \frac{n''_1}{n_1} = \frac{n'_1}{n_1}\frac{n''_1}{n'_1} = \left(\frac{K_{\mathrm{S}}}{N_{\mathrm{W}}}\omega + \frac{1}{2}\right)\left(\frac{K_{\mathrm{W}}}{N_{\mathrm{S}}}\omega^{-1} + \frac{1}{2}\right)$$

It can be easily shown that $f(1) = 1$, as expected for a neutral allele. Solving $f(\omega) = 1$ and analyzing the derivative of $f(\omega)$ shows that

$$f(\omega) \geq 1 \text{ for } \omega \leq \frac{K_{\mathrm{W}}N_{\mathrm{W}}}{K_{\mathrm{S}}N_{\mathrm{S}}} \text{ or } \omega \geq 1$$

and

$$f(\omega) < 1 \text{ for } \frac{K_{\mathrm{W}}N_{\mathrm{W}}}{K_{\mathrm{S}}N_{\mathrm{S}}} < \omega < 1.$$

Therefore, if $K_{\mathrm{S}} = K_{\mathrm{W}}$ (no change in population size), $f(\omega) > 1$ for all $\omega \neq 1$. Since $f(\omega^{-1})$ describes the change of A_2 frequency when A_2 is rare, this result means that both A_1 and A_2 alleles are positively selected when they are rare. This symmetry creates a negative frequency-dependent selection – the storage effect. However, if $K_{\mathrm{S}} > K_{\mathrm{W}}$ and $1 < \omega < \frac{K_{\mathrm{S}}N_{\mathrm{S}}}{K_{\mathrm{W}}N_{\mathrm{W}}}$, A_1 is positively selected but A_2 is not, even if A_2 is rare. This asymmetry means that A_1 is under directional selection and will eventually reach fixation. For example, if $K_{\mathrm{S}} = 2K_{\mathrm{W}}$, an allele that is a (< 2.5) times advantageous over the other allele during summer but disadvantageous by factor a^{-1} during winter is positively selected until it reaches fixation.

This result can be also interpreted in terms of alleles' "intrinsic growth rates" in the presence of refuge that increase with increasing fluctuations in their absolute fitness (eq. 5). The amplitude of fitness oscillation on the field can be given by the ratio of the maximum, $W_{x,\max}$, and the minimum, $W_{x,\min}$, within a cycle for allele

x (parameter α in eq. 5 corresponding to $\ln\left[\frac{W_{x,\max}}{W_{x,\min}}\right]/2$). In the above case with λ = 2 and $g_f = \infty$, consider a particular cycle in which the frequency of A_1 starts with p_W at the end of winter, then increases to p_S at the end of summer, and again decreases in winter. During this period, the absolute fitness of A_1 on the field reaches maximum in summer and minimum in winter: eq. (6) indicates that $W_{1,\max} = \frac{K_S}{0.5N_W}\frac{\omega}{\bar{\omega}_S}$ and $W_{1,\min} = \frac{K_W}{0.5N_S}\frac{\omega^{-1}}{\bar{\omega}_W}$, where $\bar{\omega}_S = p_W\omega + (1 - p_W)$, $\bar{\omega}_W = p_S/\omega + (1 - p_S)$, and ω is the relative fitness of A_1 in summer. Therefore,

$$\frac{W_{1,\max}}{W_{1,\min}} = \frac{K_S N_S}{K_W N_W}\frac{\bar{\omega}_W}{\bar{\omega}_S}\omega^2$$

In the same cycle, the absolute fitness of A_2 allele is $\frac{K_S}{0.5N_W}\frac{1}{\bar{\omega}_S}$ in summer and $\frac{K_W}{0.5N_S}\frac{1}{\bar{\omega}_W}$ in winter. If population size fluctuation has the stronger effect on the absolute fitness the former is the maximum, otherwise it is the latter. Then,

$$\frac{W_{2,\max}}{W_{2,\min}} = \mathrm{Max}\left[\frac{K_S N_S}{K_W N_W}\frac{\bar{\omega}_W}{\bar{\omega}_S}, \frac{K_W N_W}{K_S N_S}\frac{\bar{\omega}_S}{\bar{\omega}_W}\right]$$

It can be easily shown that $\frac{W_{1,\max}}{W_{1,\min}} > \frac{W_{2,\max}}{W_{2,\min}}$ as long as ω > 1. Therefore, the amplitude of oscillation in absolute fitness, thus the intrinsic growth rate in the presence of refuge, is always larger for A_1 than A_2 allele. It is also seen from the exact recursion with λ = 10 that, under strong density regulation (g_f = 20) the amplitudes of fluctuation in n_1 and n_2 are similar when they reach relative frequencies near 0.5 in the absence of population size fluctuation (Figure 2) but n_1 fluctuates wider than n_2 with cyclic oscillation in population size (Figure 3).

Random fluctuation of absolute fitness

Finally, it was examined whether the above results of absolute fitness-based model – directional selection for an allele causing larger fluctuation of population size and for an allele whose fitness fluctuation is positively correlated with population size fluctuation – are also true for random, rather than cyclic, fluctuation of absolute fitness. Iteration of eq. (3) was performed using the same set of parameters above. However, at each generation a random integer t^* was drawn from 1 to λ. Then, the carrying capacity and selection coefficient were given by $K_f = K_{f0}\exp\left[\beta\sin[2\pi t^*/\lambda]\right]$ and $s_t = s_{max}\sin[2\pi t^*/\lambda]$. Therefore, if β > 0 and the fitness of A_1 allele is $W_{1f} = e^{s_t}$, K_f and W_{1f} fluctuate in the same direction ($W_{1f} = K_f e^{s_{max}-\beta}/K_{f0}$): it models an allele that, for

example, leads to the immediate consumption of all available resource in the environment for reproduction rather than allocating resource evenly over successive generations. For each parameter set, 100 iterations were made and the mean frequency trajectory was obtained (Figure S2).

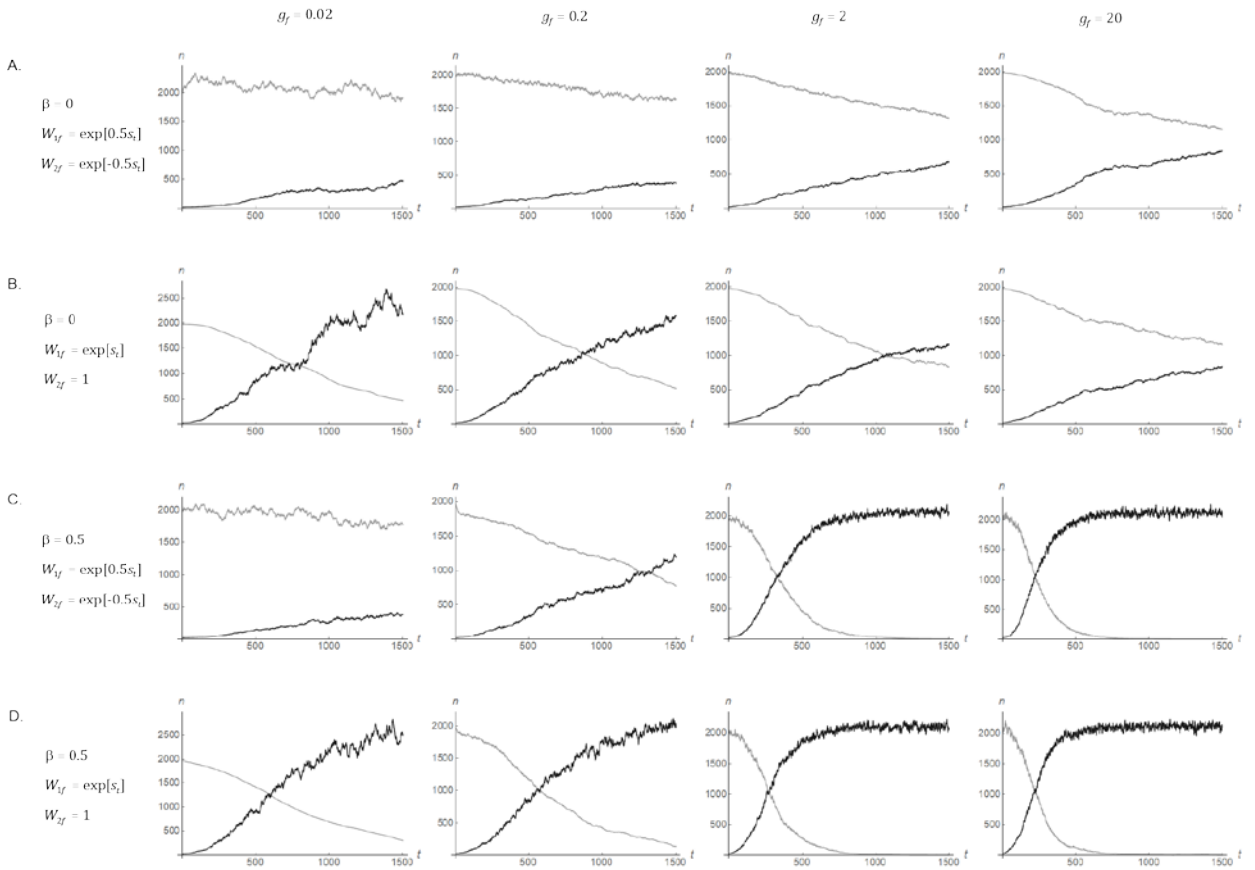

Figure S2. Changes in the absolute frequencies (n_1 and n_2) of A_1 (dark curves) and A_2 (gray curves) alleles under the random fluctuation of carrying capacity on the field ($K_{f0} = 1{,}000$, $K_f = K_{f0}\exp[\beta\sin[2\pi t^*/\lambda]]$, and $s_t = s_{max}\sin[2\pi t^*/\lambda]$, where t^* is a random integer between 1 and λ drawn each generation). Other parameters are identical to those in Figure 2.

First, with constant carrying capacity (β = 0) and symmetric absolute fitness ($W_{1f} = e^{0.5s_t}$, $W_{2f} = e^{-0.5s_t}$) the relative frequencies of A_1 and A_2 alleles change towards 0.5 (Figure S2A), which is essentially the identical result from the relative fitness-based model with random fitness fluctuation (Figure 1). However, if the absolute fitness of A_1 fluctuates but that of A_2 does not ($W_{1f} = e^{s_t}$, $W_{2f} = 1$), A_1 allele increased to fixation under weak density regulation but up to relative frequency 0.5 under strong density regulation (Figure S2B). Next, with β = 0.5, allele A_1 whose relative fitness fluctuates in the same direction with K_f was positively selected toward fixation under strong density regulation regardless of its absolute fitness (Figure S2C, D). In

summary, the dynamics of allele frequency change under random fluctuating selection on the field is qualitatively identical to that obtained under cyclically (seasonally) fluctuating selection.

Positive selection on a "deleterious" allele

So far fitness fluctuation was given by the exponential function of s_t, which oscillates symmetrically around zero, in order to maintain the geometric means of two alleles' absolute fitness at one ($\prod_t W_{1f} = \prod_t W_{2f} = 1$) on the field. The two alleles were therefore quasi-neutral. If the fitness fluctuation of two alleles are given by the linear function of s_t, namely $W_{1f} = 1 + c_1 s_t$ and $W_{2f} = 1 - c_2 s_t$, where c_1 and c_2 are constants, their geometric mean fitnesses are not identical unless $|c_1| = |c_2|$. For example, if $c_1 = 1$ and $c_2 = 0$, the geometric mean fitness of A_1 is lower than A_2: A_1 is deleterious on the field. With this change in fitness function with constant carrying capacity ($\beta = 0$), A_1 is shown to fail to be positively selected under any strength of density regulation, even if its oscillation in absolute fitness is greater than that of A_2 (Figure 4B). However, under cyclic carrying capacity ($\beta = 0.5$), A_1 replaced A_2 under strong density regulation ($g_f = 2$ or 20; Figure 4D), as the relative fitness of A_1 (W_{1f}/W_{2f}) oscillates in the same direction with the carrying capacity of the field. Namely, in the presence of refuge, fluctuation in population size can generate positive selection on an allele that otherwise would be selected against.

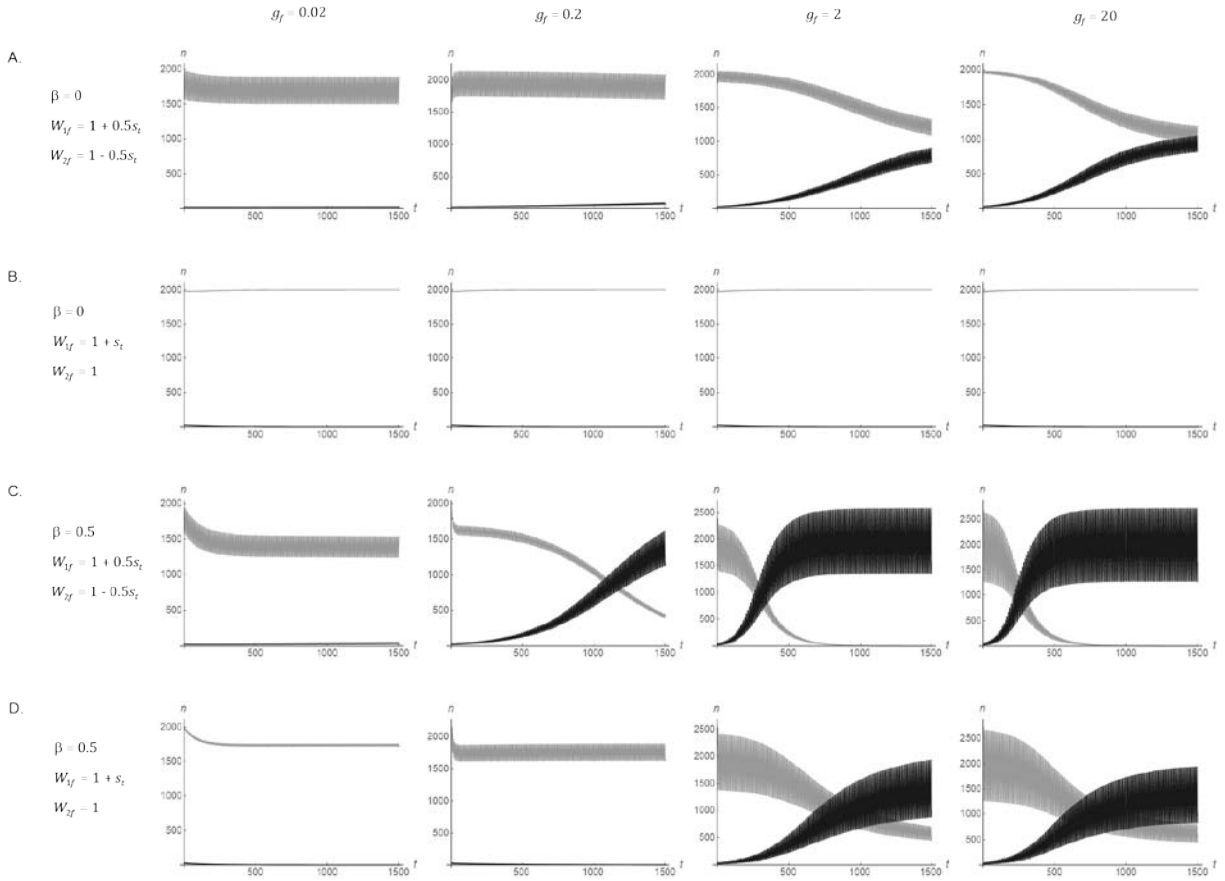

Figure 4. Changes in the absolute frequencies (n_1 and n_2) of A_1 (dark curves) and A_2 (gray curves) alleles when fitness fluctuation is given by the linear function of s_t, under constant (β = 0; A, B) and cyclically changing (β = 0.5; C, D) carrying capacity of the field. Other parameters are identical to those in Figure 3.

DISCUSSION

The model of fluctuating selection that acts on only a part of population was revised to allow the joint dynamics of population size and allele frequency changes. This simple change, specifying absolute instead of relative fitness, dramatically altered the nature of selection: under weak or moderate density regulation, positive directional selection on the allele that cause a wider fluctuation in population size emerged instead of negative frequency-dependent selection. The latter, the storage effect, has long been proposed as a mechanism for promoting species or genetic diversity (CHESSON AND WARNER 1981; BERTRAM AND MASEL 2019). Since directional selection on the allele causing wider fluctuation means that balancing selection does not operate, this study calls for significant revision of predictions in the model of storage effect. Furthermore, pre-existing fluctuation in population size was found to select an allele whose relative fitness fluctuate in the same direction. To my

knowledge, this type of selective force on alleles, which might be quasi-neutral or even deleterious (lower in geometric mean fitness) outside the refuge, generated by demographic changes was not discovered before. These results highlight the importance of investigating interactions between demographic and evolutionary genetic dynamics (KOKKO AND LÓPEZ-SEPULCRE 2007; LION 2018; GOVAERT *et al.* 2019) that is frequently ignored while ecology and evolutionary biology tend to focus on only one of them.

The fluctuation of population size, in response to either randomly or cyclically fluctuating environment, is observed in many plant and animal species, particularly for those reproducing in multiple generations over one seasonal cycle. Classical results in population genetics predicted that a genotype causing less fluctuation in fitness is favored under such an environment (GILLESPIE 1977; LANDE *et al.* 2009). Namely, they suggested that, if a trade-off occurs in the effects of a mutation such that it increases fitness in one phase of temporally changing environment and decreases it in another phase, this mutation is positively selected if the trade-off occurs in a direction decreasing the amplitude of population size fluctuation, for example by allocating resources toward a season unfavorable for the survival and/or reproduction of a species. This study, however, showed that natural selection can occur in the opposite direction if a population is partially protected from selection. Under weak or moderate density regulation, even if the population size is initially constant over time, an allele with fluctuating absolute fitness, thus causing the fluctuation of population size, is positively selected toward fixation (Figure 2B). If population size is already fluctuating due to external forces (variable environment) and/or the fixation of the above-mentioned allele at another locus, an allele causing a wider fluctuation of absolute fitness, for example by allocating further resources for a period at which the rate of growth and reproduction is already high, which inevitably causes further deterioration of fitness during the other period, can invade and therefore amplify the fluctuation of population size (Figure 3). Assuming a large number of loci at which mutations affecting life history traits can arise, one can imagine that selection at multiple loci can reinforce each other until a very wide fluctuation in population size arises.

Two topics of investigation, evolutionary bet-hedging and the Parrondo's paradox, are closely related to the model and result of this study. In the theory of evolutionary bet-hedging (SEGER AND BROCKMANN 1987; PHILIPPI AND SEGER 1989), a refuge from selection such as seed bank emerges in a reproductive strategy that may decrease the arithmetic mean but increase the geometric mean of fitness by reducing the variance of reproductive success. Namely, plants' delayed germination or insects' diapause can be the result of natural selection towards less fluctuation of fitness. In this study, however, refuge from selection is given as a fixed

demographic parameter in the model under which selection acts on variants causing different patterns of fitness fluctuation. Given the current results, findings in the previous investigation on bet-hedging may be interpreted differently. For example, fitting the field observation of annual desert plants to their mathematical model that is very similar to eq. (3) above, GREMER AND VENABLE (2014) showed that species experiencing wider fluctuation in fitness after germination have greater proportions of their population remaining in seed bank. This supports the hypothesis that delayed germination evolved as a bet-hedging strategy. However, it could be other life history traits that evolved in those species: in species with larger probability of staying in the refuge (larger seed bank), variants causing wider fitness fluctuation on the field (after germination) could have been selected.

A counter-intuitive dynamics central to the conclusion of this study – an allele that is not favored either on the field or in the refuge can be positively selected if it randomly moves between them (eq. 5) – is analogous to the behavior of other systems collectively described as Parrondo's paradox or Parrondo effect (HARMER AND ABBOTT 1999; HARMER AND ABBOTT 2002; CHEONG *et al.* 2019). In game theory, Parrondo's paradox arises when two losing games played alternatively turn into a winning game. Several biological processes were shown to yield analogous results (JANSEN AND YOSHIMURA 1998; WOLF *et al.* 2005; REED 2007; TAN AND CHEONG 2017). For example, JANSEN AND YOSHIMURA (1998), which was not initially reported as a case of Parrondo effect, showed that a population made of habitats that are ecological sinks can sustain a positive density if environment fluctuates and individuals move between habitats. CHEONG *et al.* (2019) pointed out that the common feature of biological systems yielding Parrondo effect is to have a storage in which individuals are placed for later recovery of population. Therefore, novel eco-evolutionary dynamics revealed in this study might be also considered as the result of Parrondo effect. It appears that different consequences of fluctuating selection operating heterogeneously within a population, a commonly encountered condition in nature, were focused in different investigations: the maintenance of adaptive genetic variation (storage effect), the optimization of reproductive strategy (evolutionary bet-hedging), emergence of positive growth from conditions of negative growth (Parrondo's paradox), and selection for wider population size fluctuation (this study).

Acknowledgement

This study was supported by the Research Foundation (NRF) grant 2020R1A2C1009261 funded by the Korean government.

References

Barton, N. H., 2000 Genetic hitchhiking. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 355: 1553-1562.

Bell, G., 2010 Fluctuating selection: the perpetual renewal of adaptation in variable environments. Philos Trans R Soc Lond B Biol Sci 365: 87-97.

Bergland, A. O., E. L. Behrman, K. R. O'Brien, P. S. Schmidt and D. A. Petrov, 2014 Genomic evidence of rapid and stable adaptive oscillations over seasonal time scales in Drosophila. PLoS Genet 10: e1004775.

Bertram, J., and J. Masel, 2019 Different mechanisms drive the maintenance of polymorphism at loci subject to strong versus weak fluctuating selection. Evolution 73: 883-896.

Carlson, S. M., C. J. Cunningham and P. A. Westley, 2014 Evolutionary rescue in a changing world. Trends Ecol Evol 29: 521-530.

Charlesworth, B., 1971 Selection in density-regulated populations. Ecology 52: 469-474.

Cheong, K. H., J. M. Koh and M. C. Jones, 2019 Paradoxical survival: examining the Parrondo effect across biology. BioEssays 41: 1900027.

Chesson, P. L., and R. R. Warner, 1981 Environmental variability promotes coexistence in lottery competitive systems. The American Naturalist 117: 923-943.

Dempster, E. R., 1955 Maintenance of genetic heterogeneity, pp. 25-32 in *Cold Spring Harbor Symposia on Quantitative Biology*. Cold Spring Harbor Laboratory Press.

Ellner, S., and N. G. Hairston, 1994 Role of overlapping generations in maintaining genetic variation in a fluctuating environment. The American Naturalist 143: 403-417.

Gillespie, J. H., 1977 Natural selection for variances in offspring numbers: a new evolutionary principle. The American Naturalist 111: 1010-1014.

Gillespie, J. H., 1994 *The causes of molecular evolution*. Oxford University Press.

Govaert, L., E. A. Fronhofer, S. Lion, C. Eizaguirre, D. Bonte *et al.*, 2019 Eco-evolutionary feedbacks—Theoretical models and perspectives. Functional Ecology 33: 13-30.

Grant, P. R., and B. R. Grant, 2002 Unpredictable evolution in a 30-year study of Darwin's finches. Science 296: 707-711.

Gremer, J. R., and D. L. Venable, 2014 Bet hedging in desert winter annual plants: optimal germination strategies in a variable environment. Ecol Lett 17: 380-387.

Gulisija, D., and Y. Kim, 2015 Emergence of long-term balanced polymorphism under cyclic selection of spatially variable magnitude. Evolution 69: 979-992.

Gulisija, D., Y. Kim and J. B. Plotkin, 2016 Phenotypic plasticity promotes balanced polymorphism in periodic environments by a genomic storage effect. Genetics 202: 1437-1448.

Haldane, J., and S. Jayakar, 1963 Polymorphism due to selection of varying direction. Journal of Genetics 58: 237-242.

Harmer, G. P., and D. Abbott, 1999 Parrondo's paradox. Statistical Science: 206-213.

Harmer, G. P., and D. Abbott, 2002 A review of Parrondo's paradox. Fluctuation and Noise Letters 2: R71-R107.

Hedrick, P. W., 1976 Genetic variation in a heterogeneous environment. II. Temporal heterogeneity and directional selection. Genetics 84: 145-157.

Hedrick, P. W., 1986 Genetic polymorphism in heterogeneous environments: a decade later. Annual review of ecology and systematics: 535-566.

Hedrick, P. W., 1995 Genetic polymorphism in a temporally varying environment: effects of delayed germination or diapause. Heredity 75: 164-170.

Huerta-Sanchez, E., R. Durrett and C. D. Bustamante, 2008 Population genetics of polymorphism and divergence under fluctuating selection. Genetics 178: 325-337.

Jansen, V. A., and J. Yoshimura, 1998 Populations can persist in an environment consisting of sink habitats only. Proceedings of the National Academy of Sciences 95: 3696-3698.

Kokko, H., and A. López-Sepulcre, 2007 The ecogenetic link between demography and evolution: can we bridge the gap between theory and data? Ecology Letters 10: 773-782.

Lande, R., S. Engen and B.-E. Saether, 2009 An evolutionary maximum principle for density-dependent population dynamics in a fluctuating environment. Philosophical Transactions of the Royal Society B: Biological Sciences 364: 1511-1518.

Lion, S., 2018 Theoretical approaches in evolutionary ecology: environmental feedback as a unifying perspective. The American Naturalist 191: 21-44.

Machado, H. E., A. O. Bergland, R. Taylor, S. Tilk, E. Behrman *et al.*, 2021 Broad geographic sampling reveals the shared basis and environmental correlates of seasonal adaptation in Drosophila. eLife 10.

Myers, J. H., 1988 Can a general hypothesis explain population cycles of forest Lepidoptera?, pp. 179-242 in *Advances in Ecological Research*. Elsevier.

Otto, S. P., and M. C. Whitlock, 1997 The probability of fixation in populations of changing size. Genetics 146: 723-733.

Park, Y., and Y. Kim, 2019 Partial protection from cyclical selection generates a high level of polymorphism at multiple non-neutral sites. Evolution 73: 1564-1577.

Philippi, T., and J. Seger, 1989 Hedging one's evolutionary bets, revisited. Trends in ecology & evolution 4: 41-44.

Pimentel, D., 1961 Animal population regulation by the genetic feed-back mechanism. The American Naturalist 95: 65-79.

Reed, F. A., 2007 Two-locus epistasis with sexually antagonistic selection: A genetic Parrondo's paradox. Genetics 176: 1923-1929.

Reinhold, K., 2000 Maintenance of a genetic polymorphism by fluctuating selection on sex-limited traits. Journal of Evolutionary Biology 13: 1009-1014.

Roughgarden, J., 1971 Density-dependent natural selection. Ecology 52: 453-468.

Seger, J., and H. J. Brockmann, 1987 Oxford surveys in evolutionary biology. Oxford Surveys in Evolutionary Biology 4: 182-211.

Sæther, B.-E., and S. Engen, 2015 The concept of fitness in fluctuating environments. Trends in Ecology & Evolution 30: 273-281.

Svardal, H., C. Rueffler and J. Hermisson, 2015 A general condition for adaptive genetic polymorphism in temporally and spatially heterogeneous environments. Theoretical Population Biology 99: 76-97.

Tan, Z. X., and K. H. Cheong, 2017 Nomadic-colonial life strategies enable paradoxical survival and growth despite habitat destruction. eLife 6.

Thompson, J. N., 2013 *Relentless evolution*. University of Chicago Press.

Turelli, M., D. W. Schemske and P. Bierzychudek, 2001 Stable two-allele polymorphisms maintained by fluctuating fitnesses and seed banks: protecting the blues in Linanthus parryae. Evolution 55**:** 1283-1298.

Wittmann, M. J., A. O. Bergland, M. W. Feldman, P. S. Schmidt and D. A. Petrov, 2017 Seasonally fluctuating selection can maintain polymorphism at many loci via segregation lift. Proceedings of the National Academy of Sciences 114**:** E9932-E9941.

Wolf, D. M., V. V. Vazirani and A. P. Arkin, 2005 Diversity in times of adversity: probabilistic strategies in microbial survival games. Journal of theoretical biology 234**:** 227-253.