Emergence of long-term balanced polymorphism under cyclic selection of spatially variable magnitude

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A fundamental question in evolutionary biology is what promotes genetic variation at nonneutral loci, a major precursor to adaptation in changing environments. In particular, balanced polymorphism under realistic evolutionary models of temporally varying environments in finite natural populations remains to be demonstrated. Here, we propose a novel mechanism of balancing selection under temporally varying fitnesses. Using forward-in-time computer simulations and mathematical analysis, we show that cyclic selection that spatially varies in magnitude, such as along an environmental gradient, can lead to elevated levels of nonneutral genetic polymorphism in finite populations. Balanced polymorphism is more likely with an increase in gene flow, magnitude and period of fitness oscillations, and spatial heterogeneity. This polymorphism-promoting effect is robust to small systematic fitness differences between competing alleles or to random environmental perturbation. Furthermore, we demonstrate analytically that protected polymorphism arises as spatially heterogeneous cyclic fitness oscillations generate a type of storage effect that leads to negative frequency dependent selection. Our findings imply that spatially variable cyclic environments can promote elevated levels of nonneutral genetic variation in natural populations.

KEY WORDS: Balancing selection, genetic polymorphism, population subdivision, temporally varying selection.

The maintenance of nonneutral polymorphism remains an issue of fundamental importance in population biology. Recently, a discovery of loci that harbor long-lived polymorphism has led to renewed interest in population dynamics under balancing selection (e.g., Ghosh et al. 2012; Leffler et al. 2013; Lenz et al. 2013; Bergland et al. 2014). Nevertheless, the prevalence of balancing selection and how it operates in natural populations remain unclear. Although theoretical investigations have demonstrated the feasibility of balancing selection in various models (Levene 1953; Dempster 1955; Haldane and Jayakar 1963; Gillespie 1973, 1974, 1975; Karlin and Lieberman 1974; Hoekstra 1975; Hedrick 1976, 1986, 2006; Chesson 1985; Curtsinger et al. 1994; Ellner and Hairston 1994; Ellner and Sasaki 1996; Tellier and Brown 2007), the actual contribution of proposed mechanisms to diversity in nature has been indicated only in a few well-characterized cases. Classic examples of balanced polymorphism such as plant self-incompatibility alleles point to frequency-dependent fitnesses (Charlesworth 2006), whereas the presence of sickle-cell allele in humans points to overdominance (Hedrick 2011). Recent genomic studies have implicated pathogen–host interaction in the maintenance of genomic variation (Hedrick 2011; Ghosh et al. 2012; Leffler et al. 2013; Lenz et al. 2013), largely explained by negative frequency dependent selection (Tellier and Brown 2007).

The role of temporally varying environments in the maintenance of genetic polymorphism has been a focus of numerous theoretical studies. However, so far no conclusive case of balanced polymorphism due to temporally varying selection was reported and our limited insight into this subject comes only from theory. Population genetics theory has shown that temporally varying selection maintains genetic polymorphism under the presence of
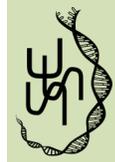
heterozygous advantage across environments (geometric mean overdominance in fitness; Dempster 1955; Gillespie 1973), overlapping generations with age/stage-specific selection or, in particular, seed banks (Ellner and Hairston 1994; Turelli et al. 2001), and density regulation with resource competition (Dean 2005; Yi and Dean 2013), or in combination with spatially varying fitnesses (Gillespie 1974, 1975; Ewing 1979). The plausibility of balanced polymorphism due to temporally varying selection has been questioned, however, as known conditions for such polymorphism were suggested to be very restrictive or nonrobust to the effects of genetic drift in finite populations (Hedrick 1976, 1986; Bull 1987; Barton and Turelli 1991; Gillespie 1991).

On the other hand, theoretical studies of species abundance in community ecology have long been proposing that temporal variation under interspecies competition can promote species coexistence under a rather general set of conditions when different fractions of populations are exposed to different selection pressures, as for example under stage-specific selection and overlapping generations, or spatial heterogeneity in selective pressure (Chesson and Warner 1981; Chesson 1985, 2000). The basic idea is that diversity persists as long as there are life-history stages or environmental patches that somewhat mitigate the effect of unfavorable environments until conditions change. Theory on this variation-promoting effect, termed "storage effect," made significant, albeit very limited and often unrecognized, impact on population genetic literature on balanced polymorphism (e.g., Ellner and Hairston 1994; Turelli et al. 2001). The storage effect due to overlapping generations also plays an essential role in recent advances in understanding adaptive phenotypic diversity maintained under heterogeneous environments (Svardal et al. 2011, 2015).

Although there is no prevailing theoretical consensus on the role of temporally varying selection in the maintenance of genetic variation, studies on biological invasions discovered an interesting pattern that suggests balanced polymorphism in temporally varying selective environments. Many invaders into novel habitats appear to have originated from temporally perturbed environments rather than from nearby stable habitats (Ricciardi and MacIsaac 2000; Lee and Gelembiuk 2008). For example, aquatic salt to fresh water invaders seem to originate from salt marshes, brackish water estuaries, or environments exposed to disturbance, where they are exposed to cyclic oscillations in salinity. Moreover, evolutionary genetic changes, rather than phenotypic plasticity alone, accompany successful survival of many populations during rapid change to new environments (Reznick and Ghalambor 2001; Phillips et al. 2006; Simons 2007; Keller and Taylor 2008; Lee and Gelembiuk 2008; Prentis et al. 2008). In addition, standing genetic polymorphism of the parental population greatly facilitates rapid adaptation to novel conditions (Gomulkiewicz and Kirkpatrick 1992; Lynch and Lande 1993; Lande and Shannon 1996; Colosimo

et al. 2005; Barrett and Schluter 2008). Therefore, rapid adaptation coinciding with the history in perturbed habitats suggests the possibility that temporally variable, in particular cyclic, selection has acted to generate and maintain nonneutral genetic diversity.

To identify novel mechanisms of balanced polymorphism under heterogeneous environments as possible explanations for the above observations, it is important to account for realistic ecological and demographic factors. In nature, it is likely that the magnitude of temporally variable selection is not uniform across a population's range, even when its direction is the same. For example, salinity tends to oscillate across seasons in a river delta, whereas salinity oscillations could be much weaker in a near-by saltwater habitat, although the peak salinity periods might coincide in both habitats. Although the effects of spatially variable selection with opposing direction on the levels of genetic polymorphism are well documented (see reviews by Felsenstein 1976; Hedrick 1976, 1986, 2006), it is not clear what patterns of polymorphism are expected in finite populations that span habitats that vary only in the magnitude of cyclic perturbations.

In this study, we demonstrate the maintenance of polymorphism in haploid finite populations under cyclic selection that varies in magnitude, but not in direction, across space, which we simply call heterogeneous cyclic selection from now on. We examine the effects of this novel mechanism of balancing selection under a very wide range of selection regimes, rates of gene flow, and population sizes, using computer simulations. Then, we perform mathematical analysis to demonstrate that negative frequency dependent selection arises in this system, although the basal fitness function is given without frequency dependence. We show that balancing selection arising under our model is a case of spatial storage effect, and that it operates in the face of genetic drift. This work will provide a foundation for future studies on the effects of such selection on linked neutral variation.

Model and Methods
EVOLUTIONARY MODEL AND SIMULATION

We employ forward-in-time simulations of evolutionary dynamics under heterogeneous cyclic selection in a subdivided population where a subpopulation exposed to oscillating environments (subpopulation 1) exchanges migrants with a subpopulation under oscillations of a smaller magnitude (subpopulation 2). At the beginning of each simulation run, a single copy of a newly introduced, that is, derived, allele randomly replaces one of the ancestral alleles either in subpopulation 1 or 2. Then, in each generation, the frequency of the derived allele is subject to the stochastic effects of gene flow (exchanging M randomly chosen migrants between subpopulations), the deterministic effect of the

cyclic selection, and the stochastic effects of reproduction in a finite population according to the Wright–Fisher model.

We use a sine function to model a cyclic selection. By allowing allelic fitness to change across a spectrum of environmental effects, we attempt to imitate the succession of effects as would occur under seasonally changing conditions such as changes in temperature, water salinity, air humidity, daylight length, or vegetation/food abundance. We employ straightforward approach to studying temporally varying selection by modeling varying fitness effects that are symmetrical for the two competing alleles. This allows easy parameterization of the model where overall neutrality or selective bias is easily specified. We assume that strong density-regulation maintains constant subpopulation sizes, N_1 and N_2, in the respective subpopulations despite severe oscillation in fitness for both alleles (thus soft selection; Wallace 1975). Therefore, the dynamics of the system is fully specified with fitness of the derived (d) relative to that of ancestral (a) allele ($w_{d,t}^{(i)}/w_{a,t}^{(i)}$), with

$$w_{d,t}^{(1)} = 1 + S^{(1)} + s_t \quad \text{and} \quad w_{a,t}^{(1)} = 1 - s_t \tag{1}$$

for subpopulation 1, and

$$w_{d,t}^{(2)} = 1 + S^{(2)} + Cs_t \quad \text{and} \quad w_{a,t}^{(2)} = 1 - Cs_t \tag{2}$$

for subpopulation 2. Here, t refers to a time given in generations, $S^{(i)}$ is a constant generating a selective advantage or disadvantage to the derived allele within subpopulation i, and C is the magnitude of fitness oscillations in subpopulation 2 relative to that in subpopulation 1, that is, the measure of spatial heterogeneity. If $C = 1$, both subpopulations experience selection of the same magnitude, and $C = 0$ implies a stable environment in subpopulation 2. Relative fitness deviation at time t due to cyclic selection is given by

$$s_t = s_{\max}\sin\left(2\pi\frac{t+r}{P}\right). \tag{3}$$

Here, $s_{\max}$ is the maximum departure from the mean fitness and P is the period (in generations) of the oscillating cycle. r is a constant for each simulation run, drawn uniformly between 0 and P. It assures that oscillations start at a random point of the sine cycle such that initial selection on the derived allele is equally likely to be negative or positive. If $S^{(1)} = 0$ and subpopulation 1 is isolated (i.e., $M = 0$), both alleles oscillate with identical geometric mean fitness over a full cycle of oscillation,

$$\left(\prod_{t=0}^{P-1}\frac{w_{d,t}^{(1)}}{w_{a,t}^{(1)}}\right)^{\frac{1}{P}} = \left(\prod_{t=0}^{P-1}\frac{1+s_t}{1-s_t}\right)^{\frac{1}{P}} = \left(\prod_{t=0}^{P-1}\frac{w_{a,t}^{(1)}}{w_{d,t}^{(1)}}\right)^{\frac{1}{P}} = 1. \tag{4}$$

The same result applies to subpopulation 2. Here, no net change in an allele frequency over the period of oscillations is

expected, making alleles quasineutral (after Hartl and Cook 1973). With $S^{(1)} \neq 0$, the derived allele is expected to produce more ($S^{(1)} > 0$) or less ($S^{(1)} < 0$) offspring than ancestral allele after each cycle of fitness oscillation, and the quasineutrality condition no longer holds.

We study evolutionary dynamics under this model via frequency-based forward-in-time computer simulations (Kim and Wiehe 2009). This method uses a random binomial number generator to emulate the stochastic change at the stage of reproduction by random gamete sampling of allele frequencies that have been changed stochastically via random sampling of migrants and deterministically by selection at each generation.

THE EFFECTS OF STOCHASTIC ENVIRONMENTS

Sine function was used to model predictably changing (e.g., seasonal) environments. However, although the seasons change predictably, the magnitude of environmental effects as well as the lengths of seasons might differ across years in nature. To probe our model under realistic natural scenarios, we mimic the stochastic effect of seasonal environmental perturbations by replacing s_t above by

$$\tilde{s}_t = \left(1 + \varepsilon_{\lfloor\frac{2t}{P}\rfloor}\right)s_t, \tag{5}$$

where the random perturbation $\varepsilon_{\lfloor\frac{2t}{P}\rfloor} \sim \text{Normal}(0,\sigma)$ is drawn independently for each half-cycle (i.e., a season), and σ approximates the expected relative within-season departure from the sine fitness function. $\varepsilon_{\lfloor\frac{2t}{P}\rfloor}$ is uniform within a season to mimic the correlated changes in the environmental effects within a season. In addition, we vary the length of seasons. Randomly, in 1 in 10 generations, the draw of $\tilde{s}_t$ according to equation (5) either jumps to two steps ahead or repeats the current step, $\tilde{s}_{t+1} = \tilde{s}_t$, effectively shortening or lengthening seasons. These perturbations to both $\tilde{s}_t$ and the length of the seasons affect the geometric mean fitnesses of alleles, making one allele more or less fit than the competing allele in a cycle of fitness oscillation even when $S^{(1)} = S^{(2)} = 0$.

MEASURES OF POLYMORPHISM

To quantify the effects of selection and demography on the levels of polymorphism in our simulations, we report several variables describing the evolutionary dynamics at the locus under selection. Primarily, we are interested in cumulative expected heterozygosity, $H = 2\text{E}\left[\sum_t p_t(1-p_t)\right]$, where p_t is the frequency of the derived allele in the population at time t and the expectation is over independent trajectories of p_t. Under neutrality, in a randomly mating population, $H = H_{\text{neutral}} = 2$ irrespective of population size (Kimura 1969). Furthermore, H can be converted to the expected diversity under recurrent mutation. If per-site mutation rate (μ) and the lengths of polymorphic trajectories are such that recurrent mutations do not interfere ($N\mu H < 1$), the expected diversity

under recurrent mutation is given by $N\mu H$ (Kimura 1969). In that case, H/H_{neutral} represents the relative level of diversity at the locus under cyclic selection compared to that under genetic drift only, with or without recurrent mutation.

The metapopulation level of diversity measured by H, however, can be inflated by population subdivision and, thus, H does not necessarily reflect the expected diversity within a subpopulation. We correct for the effects of subdivision by measuring the cumulative level of diversity expected within a random subpopulation, given by

$$H_{\text{L}} = 2\text{E}\left[\sum_t \sum_k \frac{p_{k,t}\left(1 - p_{k,t}\right) N_k}{N}\right], \quad (6)$$

where $p_{k,t}$ is the derived allele frequency after migration, selection, and reproduction in subpopulation k, N_k is the size of the subpopulation k, and N is the size of metapopulation. This measure is particularly relevant if we wish to understand the levels of diversity in invaders originating from cyclic environments, because colonization of a novel habitat is likely to involve a small group on individuals from one subpopulation, rather than a random sample from the entire population. In agreement with well-established result that the expected heterozygosity in a subpopulation is not influenced by subdivision under neutrality, H_{L} in our simulations is very close to 2 for migration rates that are not close to zero (see below).

To demonstrate that balanced polymorphism arises under spatially heterogeneous ($C < 1$) cyclic ($s_{\text{max}} > 0$) selection in finite-sized populations that are subject to genetic drift, we compare the cumulative diversity of our full model (H_{L}) to those under three baseline models. Although other parameters for population structure remain the same, we obtain the cumulative diversity (1) under neutrality ($H_{\text{L,neutral}}$), (2) in the absence of fitness oscillations ($H_{\text{L,stable}} \equiv H_{\text{L}}|_{s_{\text{max}}=0}$), that is, under a stable selective environment ($s_{\text{max}} = 0$ but for arbitrary $S^{(i)}$), and (3) under homogeneous (or spatially uniform, $C = 1$) cyclic selection ($H_{\text{L,uniform}} \equiv H_{\text{L}}|_{C=1}$). Then, if H_{L} is greater than the largest of $H_{\text{L,neutral}}$, $H_{\text{L,stable}}$, or $H_{\text{L,uniform}}$, balanced polymorphism is demonstrated.

In addition to cumulative diversity, we record the proportion, δ, of simulation runs in which polymorphism is maintained at the time of termination. From the other $K(1-\delta)$ runs, where K is the total number of simulation runs, we estimate mean times to loss and fixation. We also obtain the fixation probability as K_{F}/K, where K_{F} is the number of runs that end with fixation. These measures provided additional information on the long-term maintenance of variation independent of allele frequencies. Major mathematical symbols for model parameters and variables described so far are summarized in Table 1.

Simulation Results

Simulations were performed for a wide range of cyclic fitness effects ($s_{\text{max}} = 0.005, 0.015, 0.05, 0.15, 0.25,$ or 0.5) in combination with cycle lengths ranging from short to long ($P = 4, 8, 20, 40,$ or 100) and the relative magnitudes of selection in the second subpopulation ($C = 0, 0.2, 0.4, 0.6,$ or 0.8) with $N_2 = N_1 = 5 \times 10^4$ and reciprocal gene flow between subpopulations ($M = 1, 10, 100, 500, 1000, 10,000,$ or $25,000$ migrants per generation). The effects of spatially variable direction of selection on the levels of diversity are well documented in previous studies (Felsenstein 1976; Hedrick 1986, 2006). We, therefore, do not explore the effects of $C < 0$.

We present the results in four sections: (1) the diversity levels under the baseline models (controls), (2) the diversity levels under heterogeneous cyclic selection and quasineutrality ($S^{(1)} = S^{(2)} = 0$), (3) the effects of systematic differences in allelic fitnesses ($S^{(i)} \neq 0$), and (4) the robustness of balancing selection under stochastic environmental perturbation ($\sigma = 0.1$ or 0.2, and variable season lengths). In this section, we show that cyclic selection of spatially variable magnitude leads to long-lived balanced polymorphism under a variety of parameter combinations (Figs. 1–3). Then, in the next section, we give a formal analysis of balancing selection in our model and make a connection to the more general diversity-promoting mechanism of storage effect.

LEVELS OF DIVERSITY IN BASELINE MODELS
Stable conditions (directional selection)
In the absence of fitness oscillations, diversity levels ($H_{\text{L,stable}}$) increase when $S^{(i)} > 0$ and decrease when $S^{(i)} < 0$ compared to those under neutrality, $H_{\text{L,neutral}} = 2$ (Fig. 3, first column). The increase in diversity levels when $S^{(i)} > 0$ appears due to the considerable increase in the fixation probability. Indeed, alleles that reached fixation contribute more to the cumulative diversity than those that are quickly lost by genetic drift even when the conditional fixation time (duration of polymorphism) is reduced. The decrease in diversity levels when $S^{(i)} < 0$ appears due to a quick removal of on average disadvantageous derived allele from the population.

Homogeneous cyclic selection
In accordance with theory (see Introduction), spatially homogeneous cyclic selection ($C = 1$), with and without subdivision or with any systematic difference in mean fitness between alleles ($S^{(i)}$), does not lead to balanced polymorphism in haploid populations (results for $S^{(1)} = S^{(2)} = 0$ in Fig. 1, bottom panel). The diversity levels under homogeneous cyclic selection are typically similar to those in the absence of fitness oscillations ($H_{\text{L,uniform}} = H_{\text{L,stable}}$ or $H_{\text{L,neutral}}$), except with stronger selection (s_{max}) and longer periods of fitness oscillations (P) where $H_{\text{L,uniform}} <$

Table 1. Quick reference on major mathematical symbols and parameters used in the study.

Notation	Description
s_{max}	Fitness effect due to cyclic selection
P	Length of the oscillating fitness cycle
$S^{(i)}$	Directional selection effect of the derived allele in subpop i
C	Magnitude of fitness oscillations in subpop 2 relative to subpop 1
M	Number of migrants exchanged per generation
N_1	The size of subpopulation 1
N_2	The size of subpopulation 2
H_L	Cumulative heterozygosity under heterogeneous cyclic selection
$H_{L,neutral}$	Control 1: cumulative heterozygosity under neutrality
$H_{L,uniform}$	Control 2: cumulative heterozygosity under homogenous cyclic selection
$H_{L,stable}$	Control 3: cumulative heterozygosity under stable selective environment
δ	Proportion of loci that remained polymorphic throughout a simulation run

$H_{L,stable}$ when $S^{(i)} > 0$, while $H_{L,stable} < H_{L,uniform} < H_{L,neutral}$ when $S^{(i)} \leq 0$ ($i = 1$ and/or 2). The most prominent signature of homogenous cyclic selection is reduction in the conditional fixation time (relevant only for $S^{(i)} \geq 0$), an effect also reported by Hedrick (1974, 1976). This effect does not necessarily coincide with a reduction in the diversity levels, because shortened transit time to fixation was offset by an increase in the fixation probability under cyclic selection, except when conditional fixation time is dramatically reduced under long periods of strong selection of the same direction (long P and large s_{max}).

Given that $H_{L,uniform} \leq H_{L,stable}$ or $H_{L,neutral}$, we define balanced polymorphism due to heterogeneous cyclic selection as any H_L that exceeds $H_{L,neutral}$ ($= 2$) or $H_{L,stable}$ when $H_{L,stable} > 2$ under $S^{(i)} > 0$.

SPATIALLY VARIABLE MAGNITUDE OF CYCLIC SELECTION: BASIC MODEL

Cyclic selection of spatially heterogeneous magnitude ($C < 1$) leads to dramatically increased levels of genetic polymorphism at the locus under selection across the range of all of the four major parameters (C, P, s_{max}, and M) (Fig. 1). Diversity levels typically increase with spatial heterogeneity (lower C), and with magnitude (s_{max}) and period (P) of cyclic selection, except when the derived allele fixes fast yielding $H_L < H_{L,neutral}$ under some combinations of longer periods and strong selection in both subpopulations ($C > 0$). Here, as an allele frequency approaches its boundary, diversity is lost due to random genetic drift in finite populations.

The effect of migration rates (M) on the levels of diversity depends on the length of oscillation cycle (P), such that diversity levels tend to be highest with intermediate M when P is longer, but with highest M when P is shorter. We note that long-lived polymorphism is likely even under the levels of gene flow that made the metapopulation effectively panmictic in terms of expected ge-

netic differentiation under neutral equilibrium. Hence, although in nature some degree of subdivision with limited migration is likely to occur in populations occupying space that spans across distinct habitats, subdivision itself is not a prerequisite for the maintenance of variation under heterogeneous cyclic selection. These results are quite robust to the inequality in subpopulation sizes because we observe similar patterns of balanced polymorphism even when one subpopulation is ten times as large as the other (Fig. S1).

The relationship between diversity levels and migration rate, modulated by the length of selection cycle, can be understood as an allele's persistence depends on its migration to a more favorable habitat in the framework of storage effect (analyzed in more detail below). In rapidly changing environments, as with short P, an allele is more likely to avoid extinction if it quickly escapes to the less detrimental environment, as under large M. On the other hand, under longer P, limited migration prevents advantageous allele from swamping the environment that provides storage too quickly, preserving diversity until conditions change.

Polymorphism under recurrent mutation

Given observed $H_L >> H_{L,neutral}$, which is characterized by long-lived polymorphism, we can no longer assume that $H_L/H_{L,neutral}$ is a proxy for relative heterozygosity ($h_t/h_{t,neutral}$, where $h_t = \sum_k p_{k,t}(1 - p_{k,t})N_k/N$) under recurrent mutation (see Measures of Polymorphism). We, thus, verified that balanced polymorphism still arises in a similar parameter range under recurrent mutation with varying rates ($N\mu = 10^{-5}$–0.1, Fig. S2) as under single mutant introduction. However, the difference in heterozygosity under selection and neutrality was smaller with larger $N\mu$, obviously because, whereas the heterozygosity under neutrality increases with $N\mu$, it is already close to its upper limit under balancing selection even when mutation is rare. This makes ratio of heterozygosities ($h_t/h_{t,neutral}$) smaller with increasing $N\mu$. Moreover, when
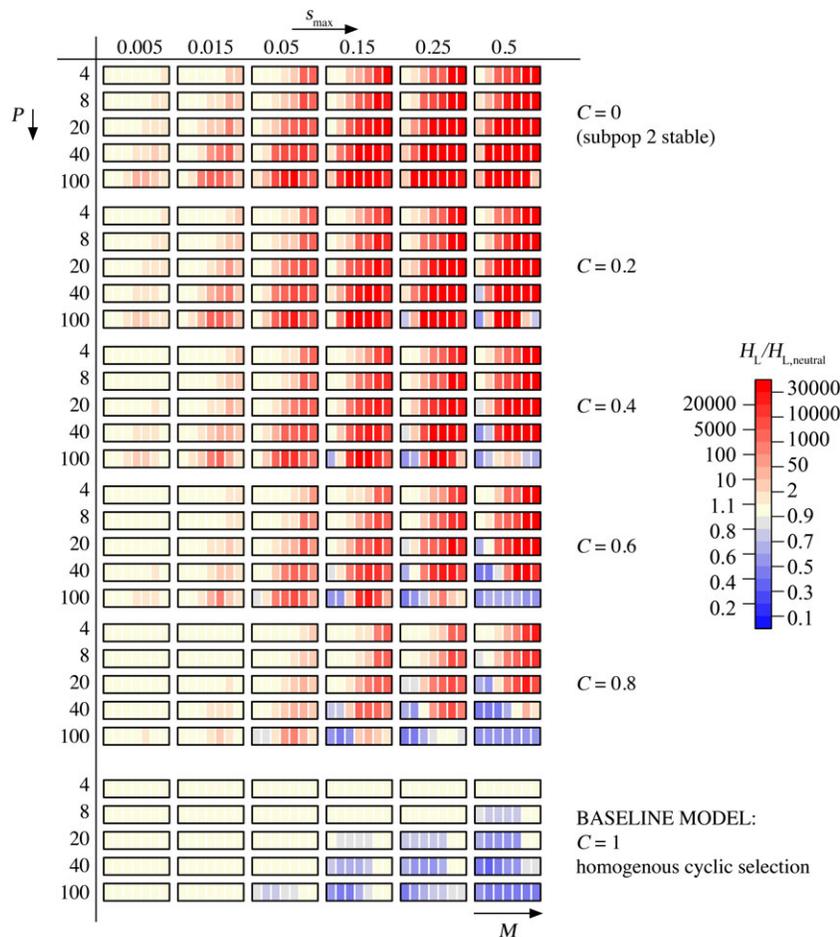
Figure 1. Diversity levels under cyclic selection of spatially variable magnitude. Cumulative diversity H_L is shown across increasing magnitude of fitness oscillations in the subpopulation 2 relative to the subpopulation 1 (C, vertically across blocks), with reference levels of H_L under homogenous cyclic selection ($C = 1$) shown in the bottom block. The magnitude (s_{max}) increases horizontally and the period (P) of fitness oscillations increases vertically within a block, while migration rate $M = [1, 10, 100, 500, 1000, 10,000, 25,000]$ varies within each minor block, all with $N_1 = N_2 = 5 \times 10^4$ and quasineutrality $S^{(i)} = 0$. We conducted $K = 10^7$ simulation runs (or 10^5 runs if H_L calculated over these exceeded 20; because such high H_L implies that a sizable proportion of alleles avoided extinction during the introductory phase), each of which ended if a loss or a fixation of the derived allele occurred or at 10^7 generations if the locus was polymorphic. Note that the color scheme describes diversity levels relative to those under genetic drift alone, such that cells in red correspond to balanced polymorphism.

reciprocal mutation is common ($N\mu = 0.01$ or 0.1), levels of diversity no longer seem to increase with s_{max}, but appear to achieve plateau at an intermediate level of selection relative within the range that we explored ($s_{max} = 0.005$–0.5). Such a high level of polymorphism with intermediate strength of selection is characterized by allele frequency oscillating within a fairly stable intermediate range (e.g., $s_{max} = 0.05$ in Fig. 2). Stronger selection ($s_{max} \geq 0.15$) can result in relatively lower level of polymorphism, as selection causes wider oscillation of allele frequencies, particularly with longer P (data not shown). Figure 2 illustrates the typical temporal pattern of long-term stable polymorphism arising under our model of heterogeneous cyclic selection: the pattern stays similar across wide, if not too low, range of recurrent mutation rates.

SYSTEMATIC DIFFERENCES IN MEAN FITNESSES BETWEEN ALLELES

Heterogeneous cyclic selection generates balanced polymorphism under systematic differences in mean fitness between the two alleles ($S^{(1)}$ and/or $S^{(2)} \neq 0$) if the differences are small compared to s_{max} (Fig. 3). Long-lived balanced polymorphism ($H_L \gg H_{L,neutral}$ or $H_{L,stable}$) is limited to a somewhat stronger cyclic selection ($s_{max} \geq 0.05$), whereas mildly elevated polymorphism is limited to $s_{max} \geq 0.015$ when $S^{(i)} = 0.01$. Maintenance of diversity is more likely when only one subpopulation is subject to systematic directional selection and the other subpopulation is under quasineutrality ($S^{(1)}$ or $S^{(2)} \neq 0$) than when both experience same directional selection ($S^{(1)} = S^{(2)} \neq 0$). Balanced polymorphism
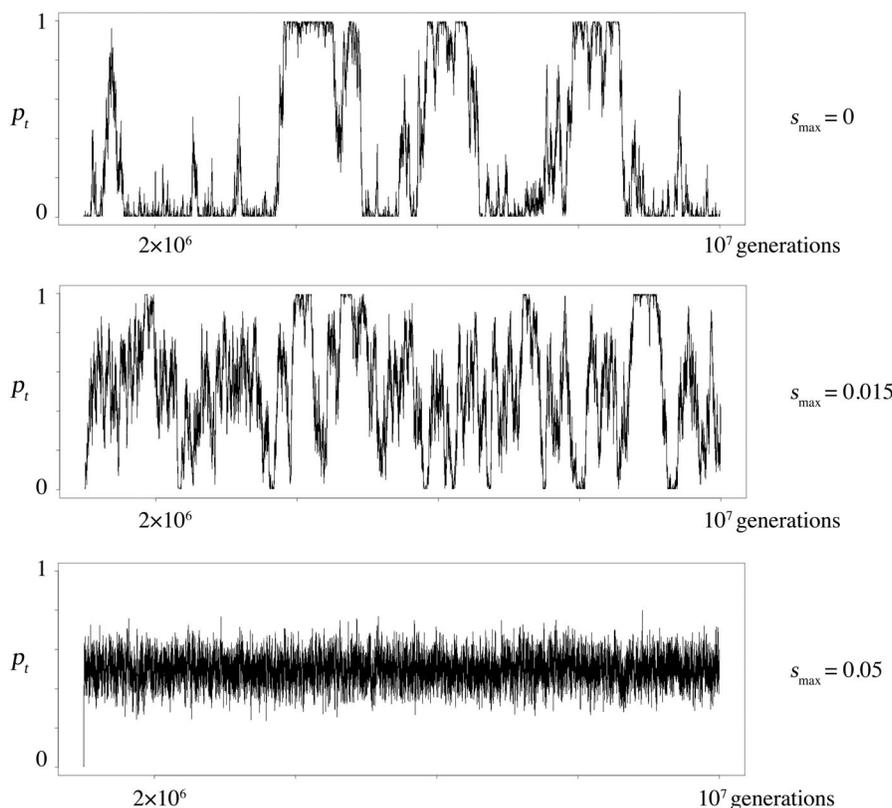
Figure 2. A sample derived allele frequency change under genetic drift alone (top) and under heterogeneous cyclic selection with $C = 0$, $S^{(i)} = 0$, $M = 25{,}000$, $P = 8$, and $s_{max} = 0.015$ (middle) or $s_{max} = 0.05$ (bottom), with recurrent reversible mutation rate $N\mu = 0.1$. Each simulation ran for 10^7 generations with $N_1 = N_2 = 5 \times 10^4$.

patterns are very similar for, on average, detrimental ($S^{(i)} < 0$) or advantageous derived allele ($S^{(i)} > 0$) and irrespective of whether the directional effect arises in the subpopulation under stronger ($S^{(1)} \neq 0$) or weaker ($S^{(2)} \neq 0$) fitness oscillations (results shown for $S^{(2)} = 0$ in Fig. 3).

A decrease in spatial heterogeneity ($C > 0$) in combination with $S^{(1)}$ and/or $S^{(2)} \neq 0$ further reduces the range of balanced polymorphism (Fig. 3). With $C = 0.8$, the levels of diversity mostly resemble those observed under homogenous cyclic selection. Here, balanced polymorphism is generally limited to mildly elevated polymorphism that occurs with $s_{max} \geq 0.05$ and $S^{(1)} = S^{(2)} = 0.01$.

ROBUSTNESS OF BALANCED POLYMORPHISM TO RANDOM ENVIRONMENTAL PERTURBATIONS

Remarkably, even under random seasonal perturbations in the magnitude of fitness oscillation ($\bar{s}_t$) and variable lengths of seasons, polymorphism persists under heterogeneous cyclic selection (Fig. S3, explored on a subset of parameters with $C = 0$ and $S^{(i)} = 0$). Moreover, balanced polymorphism occurs under a slightly wider range of parameters. It is possible that, under perturbed environments, occasional longer cycles and/or stronger

cyclic selection resulted in transiently protected polymorphism. This effect, combined with periods that do not affect diversity levels, could have resulted in an increase of expected diversity under perturbed cyclic environments in cases where the effect was absent under the basic model.

It is also worth noting that even under perturbed seasonal effects, seasons are perfectly in phase, with peaks in fitness cycles coinciding between subpopulations. Additional heterogeneity arising from seasons being slightly out of phase, a realistic natural scenario, would likely increase balanced polymorphism (Levene 1953; Svardal et al. 2015). Coupled with balanced polymorphism in the face of systematic directional selection described above, our findings here clearly suggest that long-lived balanced polymorphism under spatially heterogeneous cyclic selection is highly plausible in realistic natural populations.

Mathematical Analysis of Protected Polymorphism

Next, we obtain analytical solutions that describe the deterministic dynamics of allele frequency under our model. The major
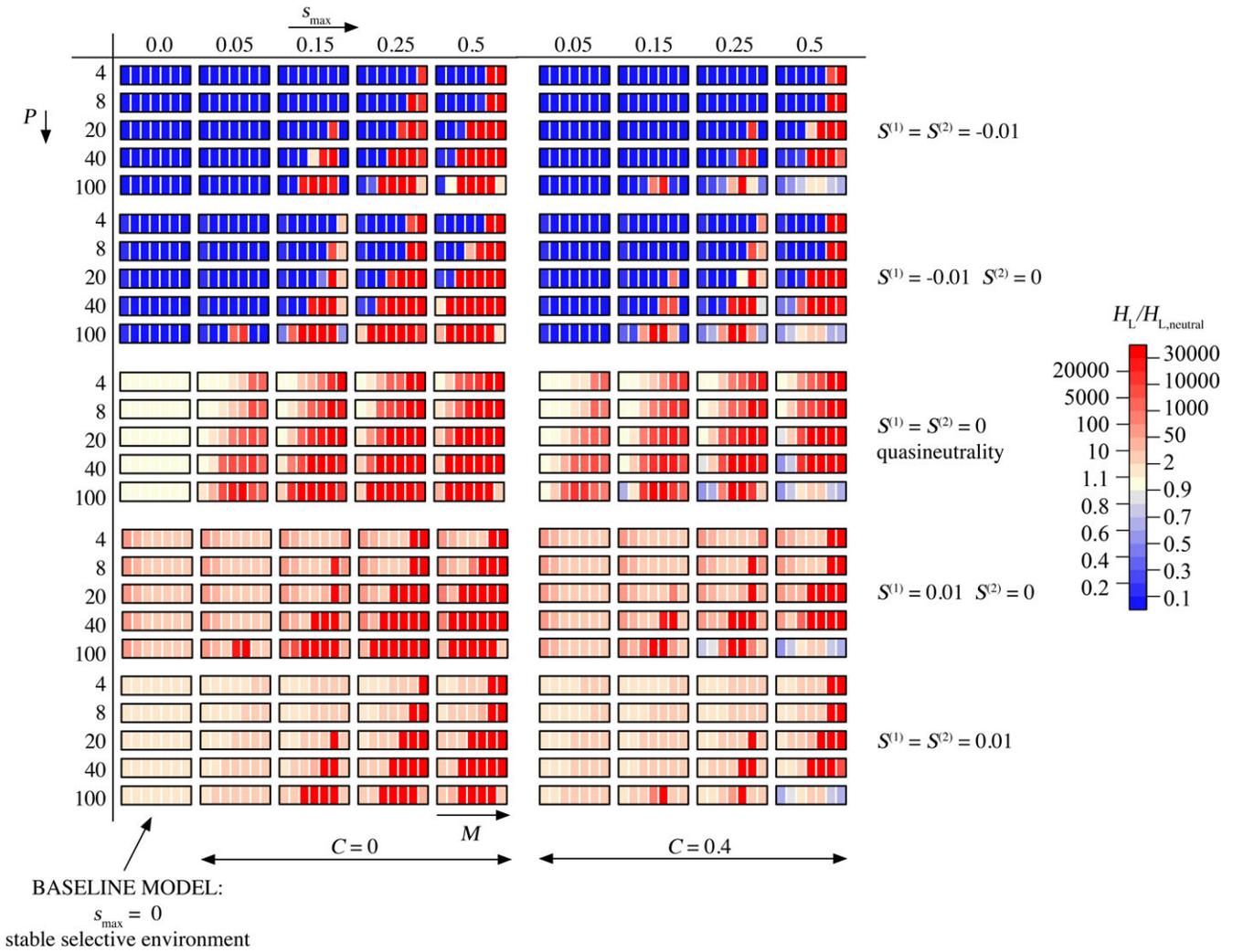
Figure 3. Diversity levels under cyclic selection of spatially variable magnitude with systematic differences between mean allelic finesses, $S^{(1)}$ in the subpopulation 1 and $S^{(2)}$ in the subpopulation 2. Cumulative polymorphism H_L is shown across increasing magnitude (s_{max}, horizontally), and period (P, vertically within a block) of fitness oscillations. Blocks corresponding to $C = 0$ are given in the left-hand side and those corresponding to $C = 0.4$ are given in the right-hand side of the figure, with the control under stable conditions (H_{stable}) given in the first column. Within each minor block migration rate $M = [1, 10, 100, 500, 1000, 10,000, 25,000]$, all with $N_1 = N_2 = 5 \times 10^4$. We conducted $K = 10^7$ simulation runs (or 10^5 runs if H_L calculated over these exceeded 20; because such high H_L implies that a sizable proportion of alleles avoided extinction during the introductory phase), each of which ended if a loss or a fixation of the derived allele occurred or at 10^7 generations if the locus was polymorphic. Note that the color scheme describes diversity levels relative to those under genetic drift alone, such that cells in red correspond to balanced polymorphism.

goal of this analysis is to demonstrate that this type of selection generates negative frequency dependence, which is commonly required for balanced polymorphism, even though our basic assignment of fitness (eqs. 1 and 2) has no frequency dependence. Due to the complexity of the model, we make a few simplifying assumptions, starting with $N_1 = N_2 = N/2$ and quasineutrality ($S^{(1)} = S^{(2)} = 0$). However, our solutions, although limited to special cases, permit the identification of a key mechanism underlying prolonged polymorphism over general parameter space.

We consider a time point when the derived allele frequencies in subpopulations 1 and 2, $p_{1,t}$ and $p_{2,t}$, are very close to zero, that is either shortly after the derived allele arises by mutation or when its frequency drifted down and, hence, polymorphism is at risk of expiring. Then, the mean fitness in subpopulations 1 and 2 at the time t is as that of common ancestral allele, $\overline{w}_t^{(i)} \approx w_{a,t}^{(i)}$. The relative change in derived allele frequency, given exactly by $w_{d,t}^{(i)}/\overline{w}_t^{(i)}$, is now approximately $w_{d,t}^{(i)}/w_{a,t}^{(i)}$. Hence, the change in allele frequencies over a generation, following migration, with

probability $m = 2M/N$ per individual, and selection, is described approximately by

$$p_{1,t+1} = \left(p_{1,t} + m\left(p_{2,t} - p_{1,t}\right)\right) \frac{w_{d,t}^{(1)}}{w_{a,t}^{(1)}}$$

$$= \left(p_{1,t} + m\left(p_{2,t} - p_{1,t}\right)\right) \frac{1 + s_t}{1 - s_t} \qquad (7)$$

and

$$p_{2,t+1} = \left(p_{2,t} + m\left(p_{1,t} - p_{2,t}\right)\right) \frac{w_{d,t}^{(2)}}{w_{a,t}^{(2)}}$$

$$= \left(p_{2,t} + m\left(p_{1,t} - p_{2,t}\right)\right) \frac{1 + Cs_t}{1 - Cs_t}. \qquad (8)$$

The frequency of the derived allele in the whole population is $X_t = (p_{1,t} + p_{2,t})/2$. Then, we are interested in whether the expected change in X_t over a cycle of fitness oscillation is positive (i.e., $X_{t+P} > X_t$), which signifies that the rare derived allele tends to increase in frequency, that is, polymorphism is promoted.

We first derive recursion for cases of no fitness oscillation in subpopulation 2 ($C = 0$). Defining $Y_t = \left(p_{1,t} - p_{2,t}\right)/2$, equations (7) and (8) are transformed to

$$X_{t+1} = \frac{1}{1 - s_t} X_t + (1 - 2m) \frac{s_t}{1 - s_t} Y_t \qquad (9)$$

and

$$Y_{t+1} = \frac{s_t}{1 - s_t} X_t + (1 - 2m) \frac{1}{1 - s_t} Y_t. \qquad (10)$$

Therefore, the expected change in X and Y over a full cycle of fitness oscillation is given by

$$\begin{pmatrix} X_{t+P} \\ Y_{t+P} \end{pmatrix} = \Lambda_{t+P-1} \cdot \Lambda_{t+P-2} \cdot \ldots \cdot \Lambda_t \begin{pmatrix} X_t \\ Y_t \end{pmatrix} \equiv \tilde{\Lambda}_t \begin{pmatrix} X_t \\ Y_t \end{pmatrix} \quad (11)$$

where

$$\Lambda_t = \begin{pmatrix} \frac{1}{1-s_t} & \frac{(1-2m)s_t}{1-s_t} \\ \frac{s_t}{1-s_t} & \frac{1-2m}{1-s_t} \end{pmatrix}. \qquad (12)$$

Below, we offer solutions to equation (11) for $P = 4$ or $m = 0.5$.

(1) Results for $C = 0$ and $P = 4$

Assume that fitness oscillates cyclically according to equation (3) with $P = 4$ and $r = 0$ (oscillations start at the beginning of a sine cycle). Therefore, $(s_0, s_1, s_2, s_3) = (0, s_{max}, 0, -s_{max})$ and

$$\tilde{\Lambda}_t = \tilde{\Lambda}_0 = \Lambda_3 \cdot \Lambda_2 \cdot \Lambda_1 \cdot \Lambda_0 = \begin{pmatrix} \frac{1-(1-2m)^2 s_{max}^2}{1-s_{max}^2} & \frac{4m(1-m)(1-2m)^2 s_{max}}{1-s_{max}^2} \\ \frac{4m(m-1)s_{max}}{1-s_{max}^2} & \frac{(1-2m)^2\left((1-2m)^2 - s_{max}^2\right)}{1-s_{max}^2} \end{pmatrix} \qquad (13)$$

for $t = kP$ ($k = 0, 1, 2, \ldots$). At the time of the mutational origin of the derived allele, as it appears randomly in subpopulation 1 or 2 and its initial frequency change is governed dominantly by random genetic drift in both subpopulations, the expectation of $p_{1,t} - p_{2,t}$ is zero. Furthermore, if M is large ($\gg 1$), frequencies at two populations will be homogenized by gene flow such that, after a certain number of generations since the introduction of the derived allele, X_t is likely to become much greater than Y_t. Similarly, the expectation of Y_t should be zero when, after reaching intermediate frequencies, $p_{1,t}$ and $p_{2,t}$ later drifted close to the boundary ($= 0$) by chance. Therefore, we may obtain the expected change in the whole-population allele frequency over a full cycle of fitness oscillation by equation (11) with $Y_t = 0$ and using equation (13). Namely,

$$X_{t+P} = \frac{1 - (1 - 2m)^2 s_{max}^2}{1 - s_{max}^2} X_t > X_t \qquad (14)$$

for $m > 0$, a rare derived allele is expected to increase in frequency over a cycle of fitness oscillation. The same result is obtained for $r = P/4$, $P/2$, and $3P/4$, namely regardless of whether the derived allele is introduced to the population during favorable or unfavorable conditions.

Note that the fraction in (14) is a weighted product of fitnesses over the cycle of fitness oscillations and the Pth root of this quantity is effectively the geometric mean fitness of the derived allele when rare. Moreover, the ancestral allele experiences the same set of fitnesses over a cycle of oscillations as the derived allele and will be subject to the same advantage (geometric mean fitness > 1) when rare. Hence, a rare allele, being ancestral or derived, will increase in frequency. This indicates negative frequency dependent selection. Moreover, X_{t+P}/X_t is an increasing function of m and is maximized at the largest possible value of m ($= 0.5$), in agreement with our simulation result of $P = 4$ shown in Figures 1 and 3. The negative frequency dependent selection increases with s_{max} over the range of values explored in this study, also in agreement with our simulation results where higher H_L is observed with increasing s_{max}.

(2) Result for $C = 0$ and $m = 0.5$

Next, we consider the case of $m = 0.5$, that is, population being fully panmictic, but with arbitrary P. It simplifies Λ_t in equation (12) and equation (11) yields

$$X_{t+P} = \left(\prod_{i=0}^{P-1} \frac{1}{1 - s_{t+i}}\right) X_t > X_t \qquad (15)$$

if $s_{max} > 0$. This result is true for arbitrary Y_t. Therefore, for an arbitrary length of fitness cycle, heterogeneous magnitude of fitness oscillation in a panmictic population is expected to

promote polymorphism by generating negative frequency dependent selection. The product $\prod_{i=0}^{P-1} \frac{1}{1-s_{t+i}}$ becomes larger as both $s_{\max}$ and P increase, corroborating the generally positive effects of $s_{\max}$ and P on the level of polymorphism identified in simulations (Figs. 1–3).

(3) Result for $C > 0$ and $m = 0.5$

Finally, we now consider a nonzero magnitude of cyclic selection in the subpopulation 2 ($C > 0$), but again effectively panmictic population. Equations (7) and (8) in this case yield

$$
\begin{aligned}
\frac{X_{t+P}}{X_t} &= \prod_{i=0}^{P-1} \left(\frac{1}{2} \frac{w_{d,t+i}^{(1)}}{w_{a,t+i}^{(1)}} + \frac{1}{2} \frac{w_{d,t+i}^{(2)}}{w_{a,t+i}^{(2)}} \right) \\
&= \prod_{i=0}^{P-1} \left(\frac{1+s_{t+i}}{2(1-s_{t+i})} + \frac{1+Cs_{t+i}}{2(1-Cs_{t+i})} \right) \\
&\geq \left(\prod_{i=0}^{P-1} \frac{1+s_{t+i}}{1-s_{t+i}} \prod_{i=0}^{P-1} \frac{1+Cs_{t+i}}{1-Cs_{t+i}} \right)^{\frac{1}{2}} = 1 \quad (16)
\end{aligned}
$$

using Jensen's inequality. Therefore, as long as $C < 1$, the condition for protected polymorphism is satisfied in panmixia.

A nonlinear combination of fitnesses that is structurally similar to that in equation (16), thus leading to the advantage of rare types, appeared in other models of species or allelic coexistence commonly described to be the result of storage effect (Chesson and Warner 1981; Chesson 1985; Ellner and Hairston 1994; Turelli et al. 2001). Equation (16) simply states that the change of allele frequency at each generation is given by equal contributions from individuals experiencing selection of large ($w_{d,t}^{(1)}/w_{a,t}^{(1)}$) and small ($w_{d,t}^{(2)}/w_{a,t}^{(2)}$) magnitudes, as a result of free migration between two subpopulations. Therefore, subpopulation 2 acts to dampen the gain (loss) of allele frequency by a good (bad) environment for the allele that would be achieved if subpopulation 1 evolves in isolation. Such dampening effect by various biological conditions is a key feature in the previous models of storage effect. However, it may not be intuitively obvious why the dampening effect confers an advantage to a rare allele, as good and bad environments for this allele still alternate in overall symmetry ($\prod w_{d,t}^{(1)}/w_{a,t}^{(1)} = \prod w_{d,t}^{(2)}/w_{a,t}^{(2)} = 1$). Chesson (1990, 2000) provided a way of graphically recognizing and understanding the nonlinearity underlying the storage effect. Below, we attempt to explain how the storage effect emerges, using arguments similar to those in Chesson and Warner (1981) and Chesson (1985) but in the more specific context of our model of spatially heterogeneous cyclic selection.

In short, when different cohorts in a population are reproduced under different selective environments, the overall change
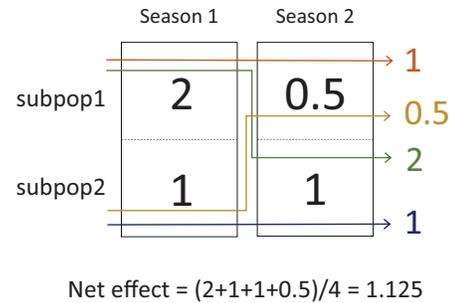

Figure 4. Numerical example of spatial storage effect under heterogeneous cyclic selection. In this simple model, there are two alternating seasons (1 and 2) and two subpopulations (subpop 1 and subpop 2) with free migration ($m = 0.5$), assuming no directional selection effect and no fitness oscillations in the second subpopulation ($S^{(i)} = 0$ and $C = 0$). The fitnesses of a rare allele in each of season–population combination are given in the four boxes. In subpop 1, the frequency of the allele is expected to double in season 1 but decrease by half in season 2 by cyclic selection, whereas there is no selection and no allele frequency change in subpop 2. The geometric mean fitness of this allele is 1 in both populations ($2 \times 0.5 = 1$ in subpop 1). However, if individuals carrying this allele stay in subpop 1 in season 1 but their offspring stay in subpop 2 in season 2, the final number of individuals increases by 2, whereas it decreases by only 0.5 for the opposite scenario. Then, expected changes along the four routes indicated by arrowed lines above $= (2 + 1 + 1 + 0.5)/4 = 1.125$. Therefore, there is net positive selection on this rare allele. Note that, even when the fitness in pop1 in season 1 decreases from 2 to 1.8, thus making this allele negatively selected in subpop 1 ($1.8 \times 0.5 = 0.9$), the presence of subpop 2 makes the overall change of allele frequency greater than 1 ($[1.8 + 0.9 + 1 + 0.5]/4 = 1.05$).

in allele frequency is much more sensitive to the increase during the good period in subpopulation 1 than to changes in other subpopulation and/or environments. Subpopulation 2 acts to store a portion of such gain so that it can be amplified in later generations when the conditions become favorable again. A simple numerical example illustrating the nature of nonlinearity is given in Figure 4. For more general analysis, we consider the subpopulation made of individuals that carry rare derived allele at generation 0 in the above scenario with $m = 0.5$ and $0 \leq C < 1$. (Here, the ancestral allele is the common allele.) Starting from these individuals, we may trace the line of descent, connecting a parent to its offspring, forward in time over P generations. Then, each line is characterized by being located in population k_t ($= 1$ or 2) at generation t. Each distinct sequence of locations across P generations is termed a path and a group of individuals sharing the same path is defined as a "lineage." We index distinct paths ($\{k_0, k_1, \ldots, k_{P-1}\} = \{1,1,\ldots,1\}, \{2,1,\ldots,1\}, \ldots,$ or $\{2,2,\ldots,2\}$) by j ($=1, \ldots, 2^P$) and let $k_t^{(j)}$ be the location ($=1$ or 2) at the tth generation

of a lineage that follows the jth path. Then, the left-hand side of equation (16) can be re-written as

$$\frac{X_{t+P}}{X_t} = \prod_{i=0}^{P-1}\left(\frac{1}{2}\rho_1(t+i) + \frac{1}{2}\rho_2(t+i)\right)$$

$$= \frac{1}{2^P}\sum_{j=1}^{2^P}\prod_{i=0}^{P-1}\rho_{k_i^{(j)}}(t+i) \equiv \frac{1}{2^P}\sum_{j=1}^{2^P}G_j. \quad (17)$$

Here, assuming that the whole population is strictly density-regulated, $\rho_k(t) = w_{d,t}^{(k)}/\overline{w}_t^{(k)} \approx w_{d,t}^{(k)}/w_{a,t}^{(k)}$ is the growth rate (absolute fitness) of a derived-allele-carrying lineage currently in location k at time t, satisfying $\prod_t \rho_1(t) = \prod_t \rho_2(t) = 1$ and $\rho_2(t) = \rho_1(t)^a$ ($0 \leq a \leq 1$, with a being an indicator of spatial heterogeneity as C in above derivations). Namely, the overall growth of derived-allele-carrying subpopulation during a cycle of environmental oscillation is the arithmetic mean of lineages' geometric fitness (cumulative growth), denoted as G_j for lineage j. If $a = 1$, the above equation becomes 1, meaning that all lineages go through a balanced temporal series of growth rates and thus experiences no change in their sizes over one cycle of environmental change (i.e., $G_j = 1$ for all j).

With $a < 1$, G_j is larger than 1 for lineages that stay more often in subpopulation 1 than 2 during the good period for the derived allele ($s_t > 0$) but more often in subpopulation 2 during the bad period ($s_t < 0$). Conversely, G_j is smaller than 1 for lineages that go through the symmetrically opposite paths. However, this deviation of G_j from 1 is asymmetric. Let $\bar{j}$ be the index of symmetrically opposite path to j, thus satisfying $G_{\bar{j}} = G_j^{-1}$. It can be easily shown that, if $G_j > 1$, $G_j - 1 > 1 - G_{\bar{j}}$. Therefore, the arithmetic mean over all G_js becomes greater than 1. In other words, due to a nonlinear spatiotemporal combination of fitnesses as in equation (17), the overall change of X_{t+P} from X_t is more sensitive to positive growth in favorable spatiotemporal environments than to loss in poor environments. Therefore, the final size of the subpopulation of individuals carrying the rare derived allele increases above the initial size after one cycle of environmental change, leading to the preservation of this allele.

This frequency-increasing effect by cyclic selection applies only to an allele that is rare. The majority of the population that carries the competing (common) allele does not experience this effect of positive growth, because their absolute fitness is close to 1 (e.g., for the ancestral allele whose frequency is assumed near 1 in the above analysis; $\rho_k = w_{a,t}^{(k)}/\bar{w}_t^{(k)} \approx 1$) across all environments and there is thus little deviation of G_j from 1. In other words, in a population under strong density regulation (soft selection), although rare alleles experience positive or negative growth as they compete mostly with common alleles, common alleles experience little change in their frequency as they compete mostly with themselves. Therefore, negative frequency dependent selection arises under our model.

The above argument further implies that the storage effect in our model does not necessarily require strict quasi-neutrality of alleles. For a given $a < 1$ (or $C < 1$), as long as the magnitude and period length of cyclic fitness oscillation are large enough to generate a wide range of G_j in the above equation, their arithmetic mean may shift above 1 even if there is systematic negative selection against a rare allele ($\prod_{t=1}^{P-1} \rho_1(t) < 1$ and/or $\prod_{t=1}^{P-1} \rho_2(t) < 1$; try to modify numbers in the example shown in Fig. 4 for quick illustration) or random perturbation to cyclic oscillations of fitness. This explains our simulation results (Figs. 3 and S3). Furthermore, this explanation of negative frequency dependent selection would apply not only for $m = 0.5$ but also for other migration rates under which different lineages or cohorts experiencing different spatiotemporal environments are generated.

In conclusion, spatially heterogeneous cyclic selection generates negative frequency dependence, which generates protected polymorphism. In a finite population, random fluctuation of allele frequency by genetic drift could override the deterministic effect of the above frequency-dependent selection, especially when the frequency is close to the boundary. Then, protected polymorphism would arise more readily in a larger population where selection is relatively stronger, in agreement with our simulation result (Fig. S1).

Discussion

Selective environments for a large number of natural populations change cyclically over time. However, the strength of cyclic selection might vary over space. Although the promotion of genetic diversity due to combined effect of temporal and spatial fluctuation in environment was suggested earlier (Ewing 1979; Chesson 1985), an explicit model of cyclic selection that varies spatially in magnitude but is of the same direction, which is far more plausible than selection of spatially changing direction, has not been investigated. We have shown not only that such spatially heterogeneous cyclic selection can lead to long-term maintenance of genetic polymorphism, but also that such polymorphism persists in spite of genetic drift in finite populations. Given a large set of parameter combinations under which balanced polymorphism occurs under our model, it is plausible that heterogeneous cyclic selection plays an important role in the maintenance of genetic polymorphism in nature. Such standing genetic polymorphism would represent a pool of readily available adaptive alleles that could greatly aid population persistence and dispersal into novel habitats (Gomulkiewicz and Kirkpatrick 1992; Colosimo et al. 2005; Barrett and Schluter 2008). Therefore, understanding the evolutionary dynamics under heterogeneous cyclic selection

may explain the origins of invaders originating from perturbed habitats.

Mathematical analysis of our model clearly demonstrates that spatial heterogeneity in cyclic selection generates negative frequency dependence that pushes rare variants into intermediate frequency, and clarifies the general roles of major model parameters, C, $s_{\max}$, P, and M, in the emergence of balanced polymorphism observed in our computer simulations. Our heuristic analysis also reveals a connection to previous studies that theorized the storage effect as a more general mechanism of promoting biological diversity. Temporal fluctuation in fitness was predicted to provide protection to rare alleles or species, but only when overlapping generations buffer the oscillating fitness effects, and thus causes the storage effect (Chesson and Warner 1981; Ellner and Hairston 1994; Chesson 1990; Turelli et al. 2001; Svardal et al. 2011). In our model of heterogeneous cyclic selection, in the absence of overlapping generations, a subpopulation with a smaller magnitude of cyclic selection plays the role of buffering environmental effects to cause a storage effect. Therefore, the polymorphism-promoting effect here can be classified as a case of the "spatial storage effect" (Chesson 1985, 2000). Note that our model assumes soft selection, where strong density regulation maintains constant size of each subpopulation (i.e., selection depends on relative not absolute fitnesses) and migration rates between subpopulations (demes' contributions to the total population) do not depend on their mean fitnesses. Given its important role in the maintenance of diversity in previous studies (Levene 1953; Chesson 1990), local competition between genotypes (density regulation) could to be crucial to the maintenance of diversity under our model of heterogeneous cyclic selection.

Balanced polymorphism occurs under heterogeneous cyclic selection provided approximate quasineutrality ($|S^{(i)}| \ll s_{\max}$; Fig. 3). Although we demonstrated emergence of underlying negative frequency dependence under a model where initial assignment of fitnesses assumes symmetry between seasons and alleles, the negative frequency dependence is not limited to such symmetry or a specific shape of a fitness function. For example, consider a modification to our model where $w_d = 1 + s_t + S^{(i)}$ and $w_a = 1$, with s_t as given in equation (3) and $S^{(i)}$ such to assure quasineutrality, that is, $\prod_{t=0}^{P-1} \left(1 + s_t + S^{(i)}\right) = 1$. Here, negative frequency dependence holds according to the argument given by equation (17). The reader can quickly verify this by numerically working out a simple two-season scenario similar to that in Figure 4. In general, promoted polymorphism will arise under cyclic selection of spatially variable magnitude as long as overall finesses of the two competing alleles are close, irrespective of the symmetry or shape of a fitness function. In nature, it is likely that the many mutations affecting the phenotype under cyclic selection are not close to quasineutral, and these mutations would not be subject

to negative frequency dependence. However, for a given trait under seasonal effects, such as changing temperature or water/soil chemistry, the number of loci in the genome that can mutate to affect related phenotypes can be very large. Then, the number of those mutations to which quasineutrality applies may not be small. Indeed, Bergland et al. (2014) found hundreds of single nucleotide polymorphism that oscillate in apparently predictable responses to seasonal temperature changes, repeating the oscillation over subsequent seasons.

In addition, we argue that nonneutral variants with strong cycling fitness effects, satisfying $s_{\max} \gg |S^{(i)}|$, could be common. Large selection coefficients are not typically considered in most population genetic models, especially in the context of adaptive evolution that leaves its footprint in genomic patterns of polymorphism and divergence (Andolfatto 2007; Jensen 2009). However, nonneutral mutations responding to temporally varying environments are likely to have much larger effect than those involved in adaptation in stable or gradually changing environments (Bell 2010), where mutations of large phenotypic effect are likely to be deleterious as the current phenotype is already close to the optimum (Orr 2005). In oscillating environments, however, a given phenotype cannot be continuously close to the optimum. A mutation of large phenotypic (thus fitness) effect can be favored while the current phenotype is away from the moving optimum. It is therefore conceivable that selection of changing direction leads to polymorphism with nonneutral alleles of quite large fitness effects. In fact, although empirical studies on varying selection are rare, there have been several reports of strong fitness oscillations at one or more loci (Lynch 1987; Cain et al. 1990; Turelli et al. 2001; Bergland et al. 2014). Mutations of strong effect, in particular, might arise in response to cycling stressors in nature, such as water salinity, temperature, anthropogenic disturbance, precipitation, etc., because these may often have very strong fitness effects and, as such, present boundaries to species geographical distributions by limiting survival in stressful environments (for a review, see Mott 2010).

Nonetheless, our knowledge about the effects of temporally varying selection in nature is still very scarce. Empirical evidence and rigorous theoretical understanding of evolution in varying environments are needed to reveal the extent and role of cyclic selection in evolution. As more genomic data become available, across species and across time points, patterns of polymorphism and adaptation in temporally variable environments will emerge.

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DATA ARCHIVING

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Diversity levels under cyclic selection of spatially variable magnitude under large and small population settings.

Figure S2. Expected heterozygosity under heterogeneous cyclic selection, h_t, relative to that under neutrality, $h_{t,\mathrm{neutral}}$, with recurrent mutation rate $N_\mu = 0.01$ (top panel) or $N_\mu = 0.1$ (bottom panel) where $N = N_1 + N_2$.

Figure S3. Diversity levels under heterogeneous cyclic selection subject to stochastic environmental perturbations and to variable season lengths.