Evolution of vertical and oblique transmission under fluctuating selection

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The evolution and maintenance of social learning, in competition with individual learning, under fluctuating selection have been well-studied in the theory of cultural evolution. Here, we study competition between vertical and oblique cultural transmission of a dichotomous phenotype under constant, periodically cycling, and randomly fluctuating selection. Conditions are derived for the existence of a stable polymorphism in a periodically cycling selection regime. Under such a selection regime, the fate of a genetic modifier of the rate of vertical transmission depends on the length of the cycle and the strength of selection. In general, the evolutionarily stable rate of vertical transmission differs markedly from the rate that maximizes the geometric mean fitness of the population. The evolution of rules of transmission has dramatically different dynamics from the more frequently studied modifiers of recombination, mutation, or migration.

periodic selection | phenotypic polymorphism | modifier theory | fitness optimum | evolutionary stability

Cavalli-Sforza and Feldman (1) distinguished two forms of nonparental phenotypic transmission in the context of cultural evolution. Horizontal transmission occurs when a trait is passed between members of the same generation and is analogous to transmission of an infectious agent. Oblique transmission to offspring is from nonparental members of the parental generation. Evolution under either of these is expected to be more rapid than under purely vertical (i.e., parent-to-offspring) transmission (2, 3).

Oblique transmission occurs via some mechanism of social learning, which may include imitation or active teaching. There has been an interesting debate over the past 30 y concerning the conditions under which social learning would have an advantage over individual learning or vertical (including genetic) transmission. This debate is usually couched in terms of the mode and tempo of environmental fluctuations that would affect fitness and hence, evolution (4–11). Mathematical analyses of models of competition between individual and social learning have generally shown that social learning has an advantage when the environment does not fluctuate too frequently. However, when environmental changes are very frequent, individual learning is favored, while innate (genetic) determination of the trait does best when periods between environmental change are long on average.

In some situations, oblique transmission of biological material is possible. In bacteria, phenotypes might be determined by heritable mobile genetic elements, such as phages (12), plasmids (13), integrons (14), and transposons (15). Similarly, some phenotypes are determined by genes that are commonly converted by uptake of foreign DNA (i.e., transformation) (16). In these cases, inheritance of a phenotype may combine vertical transmission from the parent cell and oblique transmission from other cells.

In some animals, transmission of microbes may occur during sharing or manipulation of food or other consumable resources during a social interaction. Although transmission of the microbiome in humans is likely to be mostly vertical (17), in other organisms, there is multigenerational food sharing, during which symbionts from the parental cohort may be transmitted obliquely to younger individuals (18). In such cases, fluctuations in the resource type or availability may have fitness effects that depend on features of the transmitted microbiome. This ecological perspective on community transmission is stressed by van Opstal and Bordenstein (19), who emphasize the "need to consider the relative roles of vertical and horizontal transmission of microbial communities."

Another perspective on the evolutionary consequences of fluctuating environments (and as a result, fluctuating selection) derives from the phenomenon of phenotypic switching (20–25). In these studies, mutation causes the organism to switch phenotypes (usually treated as haploid genotypes), and the problem has usually been couched in terms of the optimal rate of mutation in models where the phenotypic fitness fluctuates over time. These models did not include social learning, and the evolution was regarded as a mode of bet-hedging against future environmental change. Optimal (that is, evolutionarily stable) mutation rates depend on many features of the fluctuations (for example, degree of fitness symmetry, strength of selection, and variance in the period of fluctuation) (23).

In a recent analysis of evolution under fluctuating selection, Xue and Leibler (26) allowed an organism to absorb information about the distribution of possible environments by learning the phenotypes of members of its parental lineage from previous generations. They describe this as "positive feedback that enhances the probability that the offspring expresses the same phenotype as the parent" (26). In this formulation, there was "reinforcement of the parent phenotype" in an offspring, such as might occur through epigenetic inheritance. Although their analysis was not couched in terms of oblique and vertical transmission, as defined by Cavalli-Sforza and Feldman (1), we have been stimulated by their analysis to develop a model in which

Significance

Evolutionary dynamics of phenotypes in populations depend on how the traits are transmitted across generations and how the environments that cause selection on the traits fluctuate over time. We show that, under periodically fluctuating selection, a gene that increases the rate of vertical transmission is disfavored when the periods are short but approaches an intermediate stable rate for longer periods. This stable rate differs markedly from the rate that maximizes the geometric mean fitness. The evolution of learning rules thus differs qualitatively from the evolution of genetically modified rules of genetic transmission.

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oblique transmission, at a rate dependent on the trait frequency in the parental generation, occurs in addition to classical vertical transmission. We then ask how fluctuations in selection interact with the rate of oblique transmission to affect evolutionary dynamics and how the rate of oblique transmission itself might evolve.

In our formulation, both the parental phenotype and the distribution of phenotypes in the whole population contribute to an offspring's phenotype. Using conventional modifier theory (27), we show that, in a symmetric cyclic selection regime with cycles of periods 1 or 2, an allele reducing the rate of vertical transmission is expected to increase in frequency when rare and in so doing, to increase the mean fitness of the population. However, for cycles of greater length or period asymmetry, interesting nonmonotonicities emerge both in the uninvadable rate of vertical transmission and in the rate that maximizes the geometric time average of the population mean fitness, which we will refer to as the "geometric mean fitness." We develop the models in very large populations with cyclic selection and with random fitness and also in the case where drift occurs via sampling from generation to generation in a finite population.

Model

Consider an infinite population whose members are characterized by their phenotype ϕ, which can be of two types, $\phi = A$ or $\phi = B$, with associated frequencies x and $(1-x)$, respectively. We follow the evolution of x over discrete nonoverlapping generations. In each generation, individuals are subject to selection, where the fitnesses of A and B are w_A and w_B, respectively.

An offspring inherits its phenotype from its parent via vertical transmission with probability ρ and from a random individual in the parental population via oblique transmission with probability $(1-\rho)$. Therefore, given that the parent phenotype is ϕ and assuming uniparental inheritance (28), the conditional probability that the phenotype ϕ' of the offspring is A is

$$P(\phi' = A|\phi) = \begin{cases} (1-\rho)x + \rho & \text{if } \phi = A \\ (1-\rho)x & \text{if } \phi = B \end{cases}, \qquad [1]$$

where $x = P(\phi = A)$ in the parent's generation before selection.

Therefore, the frequency x' of phenotype A after one generation is given by the recursion equation

$$\begin{aligned} x' &= \rho\frac{w_A}{\overline{w}}x + (1-\rho)x \\ &= \frac{w_A}{\overline{w}}x\big[(1-\rho)x + \rho\big] + \frac{w_B}{\overline{w}}(1-x)\big[(1-\rho)x\big], \end{aligned} \qquad [2]$$

where $\overline{w}$ is the mean fitness, namely

$$\overline{w} = w_A x + w_B(1-x). \qquad [3]$$

Eq. **2** can be rewritten as

$$\begin{aligned} x' &= x\left[1 + \rho(1-x)\frac{w_A - w_B}{\overline{w}}\right] \\ &= x \cdot \frac{x(1-\rho)(w_A - w_B) + \rho w_A + (1-\rho)w_B}{x(w_A - w_B) + w_B}. \end{aligned} \qquad [4]$$

In what follows, we explore the evolution of the recursion Eq. **4**, namely the equilibria and their stability properties, in the cases of constant environments and changing environments.

Constant Environment. When the environment is constant, the fitness parameters w_A and w_B do not change between generations, and we have the following result.

Result 1. *If $0 < \rho \le 1$ and both w_A and w_B are positive with $w_A \neq w_B$, then fixation in the phenotype A (B) is globally stable when $w_A > w_B$ ($w_A < w_B$).*

Proof: If we rewrite Eq. **4** as $x' = x \cdot f(x)$, it can be seen that $f(1) = 1$, and for $\rho > 0$ and $0 < x < 1$,

$$\begin{aligned} f(x) > 1 \quad &\text{when} \quad w_A > w_B, \\ f(x) < 1 \quad &\text{when} \quad w_A < w_B. \end{aligned} \qquad [5]$$

Hence, as $w_A > 0$ and $w_B > 0$, both fixations in A or in B ($x^* = 1$ for fixation in A and $x^* = 0$ for fixation in B) are equilibrium points of Eq. **4**. Moreover, if x_t is the value of x at the tth generation $(t = 0, 1, 2, \dots)$, from Eqs. **4** and **5**, we have, for any $0 < x_0 < 1$ and all $t = 0, 1, 2, \dots$,

$$\begin{aligned} x_{t+1} > x_t \quad &\text{when} \quad w_A > w_B, \\ x_{t+1} < x_t \quad &\text{when} \quad w_A < w_B, \end{aligned} \qquad [6]$$

and since $x^* = 1$ or $x^* = 0$ is the only equilibrium point, we have

$$\begin{aligned} &\lim_{t\to\infty} x_t = 1, \quad \text{for all } 0 < x_0 \le 1, \quad \text{when } w_A > w_B, \\ &\lim_{t\to\infty} x_t = 0, \quad \text{for all } 0 \le x_0 < 1, \quad \text{when } w_A < w_B. \end{aligned} \qquad [7]$$

Therefore, fixation of the favored phenotype is globally stable.

Periodically Changing Environment. Suppose the environment changes periodically, such that the favored phenotype changes after a fixed number of generations. Simple examples are $A1B1 = ABABAB\dots$, in which the favored phenotype switches every generation, or $A2B1 = AABAABAAB\dots$, where every two generations, in which selection favors A, are followed by a single generation, in which selection favors B. In general, $AkBl$ denotes a selection regime, in which the period is of $(k+l)$ generations, with k generations favoring phenotype A followed by l generations favoring B.

Let W be the fitness of the favored phenotype and w be that of the other phenotype, where $0 < w < W$. Rewrite Eq. **4** as $x' = F_A(x) = xf_A(x)$ when A is favored and $x' = F_B(x) = xf_B(x)$ when B is favored. Then,

$$\begin{aligned} f_A(x) &= \frac{x(1-\rho)(W-w) + \rho W + (1-\rho)w}{x(W-w) + w} \\ &= 1 + \rho(1-x)\frac{W-w}{Wx + w(1-x)}, \\ f_B(x) &= \frac{x(1-\rho)(w-W) + \rho w + (1-\rho)W}{x(w-W) + W} \\ &= 1 + \rho(1-x)\frac{w-W}{wx + W(1-x)}. \end{aligned} \qquad [8]$$

If x_t denotes the frequency of the phenotype A at generation t starting with x_0 initially, then as we are interested in the values of x_t for $t = n(k+l)$ with $n = 0, 1, \dots$ at the end of complete periods, we can write

$$x_{(n+1)(k+l)} = F(x_{n(k+l)}), \quad n = 0, 1, 2, \dots, \qquad [9]$$

where F is the composed function

$$F = \underbrace{F_B \circ F_B \circ \cdots \circ F_B}_{l \text{ times}} \circ \underbrace{F_A \circ F_A \circ \cdots \circ F_A}_{k \text{ times}}. \qquad [10]$$

Clearly, since $F_A(0) = F_B(0) = 0$ and $F_A(1) = F_B(1) = 1$, both fixations in A or in B are equilibrium points. An interesting question is when these fixations are locally stable. We concentrate on $x^* = 0$, the fixation of the phenotype B. As $x' = F_A(x) = xf_A(x)$ for k generations and $x' = F_B(x) = xf_B(x)$ for l generations, the linear approximation of $F(x)$ "near" $x = 0$ is

$$F(x) \simeq \big[f_A(0)\big]^k \big[f_B(0)\big]^l x. \qquad [11]$$

Hence, the local stability of $x^*=0$ is determined by the product $[f_A(0)]^k[f_B(0)]^l$; $x^*=0$ is locally stable if this product is less than one and unstable if it is larger than one.
From Eq. **8**, we have

$$f_A(0)=1+\rho\frac{W-w}{w},\qquad f_B(0)=1+\rho\frac{w-W}{W}. \quad \textbf{[12]}$$

We start with the case $k=l$.

Result 2. *If $k=l$ and $0<w<W$ with $0<\rho<1$, fixation of B is unstable.*

Proof: The local stability of $x^*=0$, the fixation of B, is determined by the product

$$[f_A(0)]^k[f_B(0)]^k=\left[\left(1+\rho\frac{W-w}{w}\right)\left(1+\rho\frac{w-W}{W}\right)\right]^k. \quad \textbf{[13]}$$

Observe that

$$\left(1+\rho\frac{W-w}{w}\right)\left(1+\rho\frac{w-W}{W}\right)=1+\rho(1-\rho)\frac{(W-w)^2}{wW}>1. \quad \textbf{[14]}$$

Since $0<\rho<1$ and $0<w<W$, fixation on B is unstable.

Conclusions.

i) Since $k=l$ and the above result also holds when $0<W<w$, there is total symmetry between the two fixations in A and B, and fixation in A is also unstable. Thus, neither phenotype can be lost, and there is a protected polymorphism (29).
ii) For general k, l, the condition for local stability of fixation in A is

$$[f_A(0)]^l[f_B(0)]^k<1, \quad \textbf{[15]}$$

and that of B is

$$[f_A(0)]^k[f_B(0)]^l<1. \quad \textbf{[16]}$$

Therefore, following *Result 2*,

$$[f_A(0)]^{k+l}[f_B(0)]^{k+l}>1, \quad \textbf{[17]}$$

and it is impossible that both fixations are stable. Furthermore, since by Eq. **12**, $f_A(0)>1$ and $0<f_B(0)<1$ when $0<w<W$, by choosing k and l appropriately, fixation on A or fixation on B (but not both) can be stable. In addition, we can have both fixations unstable giving the following result.

Result 3. *With $0<\rho<1$ and $0<w<W$ in the case of $AkBl$ periodically changing environments, both fixations may be unstable, producing a protected polymorphism.*

Proof: Let $a=1+\rho\frac{W-w}{w}$ and $b=1+\rho\frac{w-W}{W}$, and our assumption entails $a>1$ and $0<b<1$. Following Eq. **11**, fixation in B is unstable if $a^kb^l>1$, and similarly, fixation in A is unstable if $a^lb^k>1$. Therefore, both fixations are unstable if

$$a^kb^l>1 \quad \text{and} \quad a^lb^k>1 \quad \textbf{[18]}$$

or equivalently, if

$$k\log a+l\log b>0 \quad \text{and} \quad l\log a+k\log b>0. \quad \textbf{[19]}$$

Now the inequalities of Eq. **19** hold if and only if

$$k\frac{\log(1/b)}{\log a}<l<k\frac{\log a}{\log(1/b)}. \quad \textbf{[20]}$$

These inequalities are consistent if and only if $\log(1/b)<\log a$ (i.e., $ab>1$), which is true by Eq. **14**.

The linear approximation of $F(x)$ near $x^*=0$ (Eq. **11**) does not depend on the order in which phenotypes A and B are favored within a cycle of $k+l$ generations. Therefore, the local stability properties of the two fixations depend only on the fact that, in a cycle of $(k+l)$ generations, A is favored k times and B is favored l times and not their order in the cycle. When neither fixation in A nor that in B are stable, there is a protected polymorphism, and we expect to have one or more polymorphic equilibria. Fig. S1 illustrates the relationship between k, l and ρ that gives polymorphism of A and B, or fixation, for different values of $s=W-w$.

For the simple case of $A1B1$ periodically changing environment, we have the following.

Result 4. *In the case $A1B1$ with $0<\rho<1$ and $0<w<W$, the two fixations are unstable, and there exists a unique stable polymorphism.*

Proof: Let x be the initial frequency of A and x' be its frequency after one cycle of $A1B1$ selection. Then, $x'=F_B(F_A(x))$, where, by Eq. **8**,

$$F_A(x)=x\frac{x(1-\rho)(W-w)+\rho W+(1-\rho)w}{x(W-w)+w},$$
$$F_B(y)=y\frac{y(1-\rho)(w-W)+\rho w+(1-\rho)W}{y(w-W)+W}. \quad \textbf{[21]}$$

The equilibrium equation is $x=F_B(F_A(x))$, which reduces to a fourth degree polynomial equation in x. Since the fixations in B and A are equilibria corresponding to the solutions $x=0$ and $x=1$, the other equilibria correspond to solutions of a quadratic equation $Q(x)=\alpha_2x^2+\alpha_1x+\alpha_0=0$, with $\alpha_2=1$ and

$$\alpha_1=\frac{W+w}{(2-\rho)(W-w)}-1,\ \alpha_0=\frac{-w}{(2-\rho)(W-w)}. \quad \textbf{[22]}$$

As $0<\rho<1$ and $0<w<W$, we have

$$Q(0)=\frac{-w}{(2-\rho)(W-w)}<0$$
$$\text{and}\ \ Q(1)=\frac{W}{(2-\rho)(W-w)}>0. \quad \textbf{[23]}$$

Also, as $\alpha_2=1$ and $\alpha_0<0$, the quadratic equation $Q(x)=0$ has two real roots, one negative and one positive x^*, satisfying $0<x^*<1$. The latter determines a unique polymorphism. Let $H(x)=F_B(F_A(x))$. Then,

$$H(0)=0,\quad H(x^*)=x^*,\quad H(1)=1. \quad \textbf{[24]}$$

Also,

$$F_A'(x)=\frac{x^2(1-\rho)(W-w)^2+2xw(1-\rho)(W-w)+w[\rho W+(1-\rho)w]}{[x(W-w)+w]^2} \quad \textbf{[25]}$$

and

$$F_B'(x)=\frac{x^2(1-\rho)(w-W)^2+2xW(1-\rho)(w-W)+W[\rho w+(1-\rho)W]}{[x(w-W)+W]^2}. \quad \textbf{[26]}$$

From our assumptions on ρ, w, and W, we have $F'_A(x) > 0$ for $0 \le x \le 1$. Observe that the numerator of $F'_B(x)$ is linear in ρ; its value when $\rho = 1$ is $wW > 0$, and when $\rho = 0$, it is

$$x^2(w - W)^2 + 2xW(w - W) + W^2 = [x(w - W) + W]^2 > 0. \quad [27]$$

Hence, $F'_B(x) > 0$ for all $0 \le x \le 1$, and $H'(x) = F'_B(F_A(x))\, F'_A(x)$ is positive when $0 \le x \le 1$. Thus, $H(x)$ is monotone increasing for $0 \le x \le 1$; $H(x) > x$ is monotone increasing for $0 < x < x^*$, and $H(x) < x$ is monotone increasing for $x^* < x < 1$. Starting from any initial value $0 < x_0 < 1$, we have $x_t \to x^*$ as $t \to \infty$. Fig. S2 *A*, *C*, and *E* illustrates how the frequency of A changes over time in the $A1B1$ regime of cycling selection.

For more general cyclic fitness regimes, the polynomial that gives the equilibria is of higher order, and it is conceivable that more than one stable polymorphism could exist for given values of ρ, W, and w. We have been able to show that, when neither fixation in A nor fixation in B are stable, in the $AkBk$ case, this cannot occur. In fact, we have the following.

Result 5. *In the $AkBk$ selection regimes, if the fixations in A and B are locally unstable, a single stable polymorphic equilibrium exists.*

The proof of *Result 5* is in *SI Text*. Fig. S3*A* shows the stable equilibrium frequencies x^* as a function of ρ, W, and w in the $A1B1$ regime. For $AkBk$ selection regimes from $k = 1$ to $k = 40$, Fig. S4 illustrates the convergence to a single stable polymorphism.

We have not been able to prove that, for selection regimes $AkBl$ with $l \ne k$, there is a single stable polymorphic equilibrium when the two fixations are unstable. However, the numerical examples in Fig. S1 for $AkBl$ and in Fig. 1 and Fig. S5 for the special case $A1B2$ all exhibit a single stable polymorphic equilibrium when fixations in A and B are unstable. These numerical results suggest that, for $W > w > 0$ and $0 < \rho < 1$, the high-order equilibrium polynomial has only a single root corresponding to a globally stable polymorphism. Fig. S6 shows that this is the case for the $A3B10$ regime.

Randomly Changing Environment. We now consider the case where the environment changes according to a stochastic process. Without loss of generality, assume that the fitness parameters at generation t ($t = 0, 1, 2, \dots$) are $1 + s_t$ for phenotype A and 1 for phenotype B, where the random variables s_t for $t = 0, 1, 2, \dots$ are independent and identically distributed. Also assume that there are positive constants C and D, such that $P(-1 + C < s_t < D) = 1$.

Corresponding to Eq. **4**, with $w_A = 1 + s_t$ and $w_B = 1$, the recursion equation is

$$x_{t+1} = x_t \frac{1 + \rho s_t + x_t(1 - \rho)s_t}{1 + x_t s_t} \quad t = 0, 1, 2, \dots. \quad [28]$$

As $\{x_t\}$ for $t = 0, 1, 2, \dots$ is a sequence of random variables, the notion of stability of the two fixation states needs clarification. Following Karlin and Lieberman (30) and Karlin and Liberman (31), we make the following definition.

Definition: "Stochastic local stability" is defined as follows. A constant equilibrium state x^* is said to be stochastically locally stable if, for any $\varepsilon > 0$, there exists a $\delta > 0$, such that $|x_0 - x^*| < \delta$ implies

$$P\left(\lim_{t\to\infty} x_t = x^*\right) \ge 1 - \varepsilon. \quad [29]$$

Thus, x^* is stochastically locally stable if for any initial x_0 sufficiently near x^* the process x_t converges to x^* with high probability.

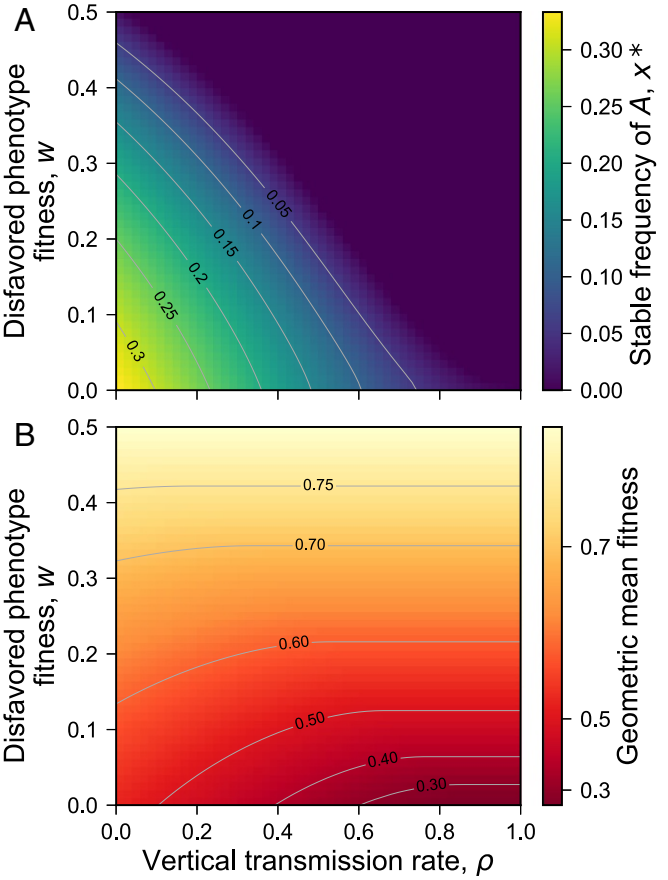

Fig. 1. Stable frequency of phenotype *A* and geometric mean fitness in selection regime *A1B2* as a function of the vertical transmission rate ρ and the fitness of the disfavored phenotype *w*. (*A*) Stable frequency of phenotype *A* at the end of each three-generation cycle. (*B*) Geometric average of the stable population mean fitness over the three-generation cycle: $(\overline{w}^* \cdot \overline{w}^{**} \cdot \overline{w}^{***})^{1/3}$. Gray contour lines join ρ and *w* combinations that result in the same stable value. In all cases, $W = 1$.

In our case, there are two constant equilibria $x^* = 0$ and $x^* = 1$ corresponding to fixation in B and A, respectively. We can characterize the stochastic local stability of these fixations with the following results, and proofs are in *SI Text*.

Result 6. *Suppose $E[\log(1 + \rho s_t)] > 0$. Then, $x^* = 0$, the fixation of phenotype B, is not stochastically locally stable. In fact, $P(\lim_{t\to\infty} x_t = 0) = 0$.*

Result 7. *Suppose $E[\log(1 + \rho s_t)] < 0$. Then, $x^* = 0$, the fixation of phenotype B, is stochastically locally stable. In particular, if $E(s_t) \le 0$, $x^* = 0$ is stochastically locally stable.*

Using the general notation for the fitness parameters w_A and w_B, the stochastic local stability of fixation in B is determined by the sign of $E\left[\log\left(1 - \rho + \rho\frac{w_A}{w_B}\right)\right]$, and that of fixation in A is determined by the sign of $E\left[\log\left(1 - \rho + \rho\frac{w_B}{w_A}\right)\right]$. For example, if the sign of the first is negative, fixation in B is stochastically locally stable, and when it is positive, with probability of one, convergence to fixation in B does not occur. It is also true that, if $E(w_A/w_B) \le 1$, then fixation of B is stochastically locally stable. Following Eq. **14**, for all realizations of w_A and w_B,

$$\log\left(1 - \rho + \rho\frac{w_A}{w_B}\right) + \log\left(1 - \rho + \rho\frac{w_B}{w_A}\right) > 0. \quad [30]$$

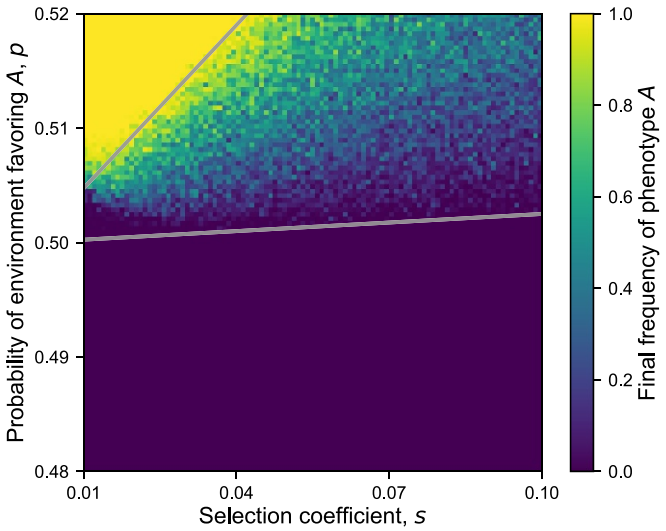

Fig. 2. Stochastic local stability. The figure shows the frequency of phenotype A after 10^6 generations in a very large population evolving in a stochastic environment (Eq. **28**). The fitnesses of phenotypes A and B are $w_A = 1 + s_t$ and $w_B = 1$, respectively, where s_t is s with probability p and $-s$ with probability $1 - p$. The gray lines mark combinations of p and s for which $E[\log(1 - \rho + \rho\frac{w_A}{w_B})] = 0$ and $E[\log(1 - \rho + \rho\frac{w_B}{w_A})] = 0$. According to *Result 6*, between these lines, fixation of either phenotype is not stochastically locally stable, and we expect a stationary polymorphism between the lines. Here, initial frequency of A is $x_0 = 1/10,000$, and the vertical transmission rate is $\rho = 0.1$.

Therefore, as in the case of periodically changing environments $AkBl$, it is impossible that both fixations are simultaneously stochastically locally stable. It is possible, however, that neither fixation is stochastically locally stable, in which case, we expect the population to converge to a polymorphic distribution. Fig. 2 illustrates how the properties of s_t in Eq. **28** affect the frequency of phenotype A and in particular, the stochastic local stability of fixation in phenotype B. Fig. 3 shows the dynamics of the frequency of A in a case where w_A and w_B are identically distributed and independent; in this case, the expectation of the stationary distribution is $\frac{1}{2}$, and its variance increases as ρ increases.

Evolutionary Stability of Oblique Transmission

An interesting question concerns the evolution of oblique transmission itself. For example, is there an evolutionarily stable rate of oblique transmission? To answer this question, we use a modifier model, in which we suppose that the vertical transmission rate is controlled by a genetic locus with two possible alleles m and M. Let the vertical transmission rates determined by m and M be ρ and P, respectively. Thus, there are four pheno-genotypes: mA, mB, MA, and MB, with frequencies that, at a given generation, are denoted by x_1, x_2, x_3, and x_4, respectively. As the fitnesses are determined by the two phenotypes A and B and the modifier locus is selectively neutral, we have the following table:

pheno-genotype	mA	mB	MA	MB
frequency	x_1	x_2	x_3	x_4
fitness	w_A	w_B	w_A	w_B
vertical transmission rate	ρ	ρ	P	P

. **[31]**

Following the rationale leading to Eq. **2**, the next generation pheno-genotype frequencies x_1', x_2', x_3', and x_4' are

$$\begin{aligned}
\overline{w}x_1' &= w_A x_1\left[(1-\rho)(x_1+x_3)+\rho\right] + w_B x_2(1-\rho)(x_1+x_3)\\
\overline{w}x_2' &= w_A x_1(1-\rho)(x_2+x_4) + w_B x_2\left[(1-\rho)(x_2+x_4)+\rho\right]\\
\overline{w}x_3' &= w_A x_3\left[(1-P)(x_1+x_3)+P\right] + w_B x_4(1-P)(x_1+x_3)\\
\overline{w}x_4' &= w_A x_3(1-P)(x_2+x_4) + w_B x_4\left[(1-P)(x_2+x_4)+P\right],
\end{aligned} \quad \textbf{[32]}$$

with $\overline{w}$, the mean fitness, given by

$$\overline{w} = w_A(x_1+x_3) + w_B(x_2+x_4). \quad \textbf{[33]}$$

Note that, under these assumptions, the M/m locus and the A/B phenotypic dichotomy do not undergo anything analogous to recombination, which might be introduced if A/B phenotypes were viewed as haploid genetic variants.

Starting with a stable equilibrium, where only the m allele is present, we check its external stability (27, 32) to invasion by allele M. A constant environment always leads to fixation of the favored type, independent of ρ. We, therefore, assume changing environments and in particular, the simple case of the $A1B1$ cycling environment, where a unique stable polymorphism exists and depends on ρ (*SI Text* has a computational analysis of the general $AkBl$ case). Specifically, from Eq. **32** with $w_A = W$, $w_B = w$ in the first generation and $w_A = w$, $w_B = W$ in the second generation, after two generations, we have

$$\underline{x}'' = T_2(T_1\underline{x}), \quad \textbf{[34]}$$

where the nonlinear transformation $\underline{x}' = T_1\underline{x}$ is given by Eq. **32** with $w_A = W$, $w_B = w$ and the nonlinear transformation $\underline{x}'' = T_2\underline{x}'$ is given by Eq. **32** with $w_A = w$, $w_B = W$. Here, $\underline{x}$, $\underline{x}'$, and $\underline{x}''$ are the frequency vectors.

For the $A1B1$ case, when only the m allele is present with associated rate ρ, $0 < \rho < 1$, and $0 < w < W$, a unique stable equilibrium $\underline{x}^* = (x_1^*, 1 - x_1^*, 0, 0)$ exists. x_1^* is the only positive root of the quadratic equation $Q(x) = \alpha_2 x^2 + \alpha_1 x + \alpha_0 = 0$, with $\alpha_2, \alpha_1, \alpha_0$ specified in Eq. **22**. Solving $Q(x) = 0$ gives

$$x_1^* = \frac{1}{2} - \frac{W + w - \sqrt{(1-\rho)^2(W-w)^2 + 4Ww}}{2\cdot(2-\rho)(W-w)}, \quad \textbf{[35]}$$

and it can be seen that

$$\frac{\sqrt{Ww} - w}{W - w} < x_1^* < \frac{1}{2}. \quad \textbf{[36]}$$

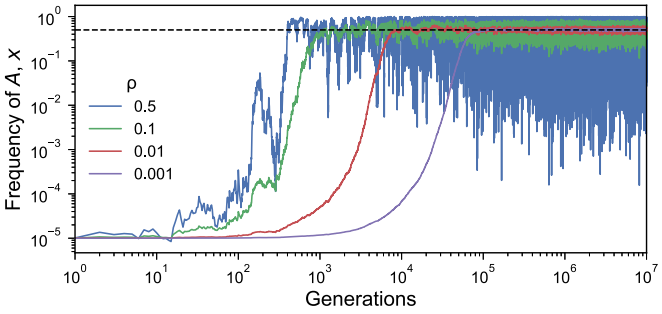

Fig. 3. Effect of vertical transmission rate ρ on phenotype polymorphism in a randomly changing environment. Dynamics of the frequency of phenotype A over time starting at $x_0 = 10^{-5}$ when the fitnesses of phenotypes A and B are identically and independently distributed random variables. As the vertical transmission rate ρ increases from 0.001 to 0.5, the frequency reaches a polymorphic distribution with $E(x_t) \to 0.5$ faster, but the variance also increases. The fitnesses of phenotypes A and B, w_A and w_B, respectively, are both exponential random variables with expected values of two.

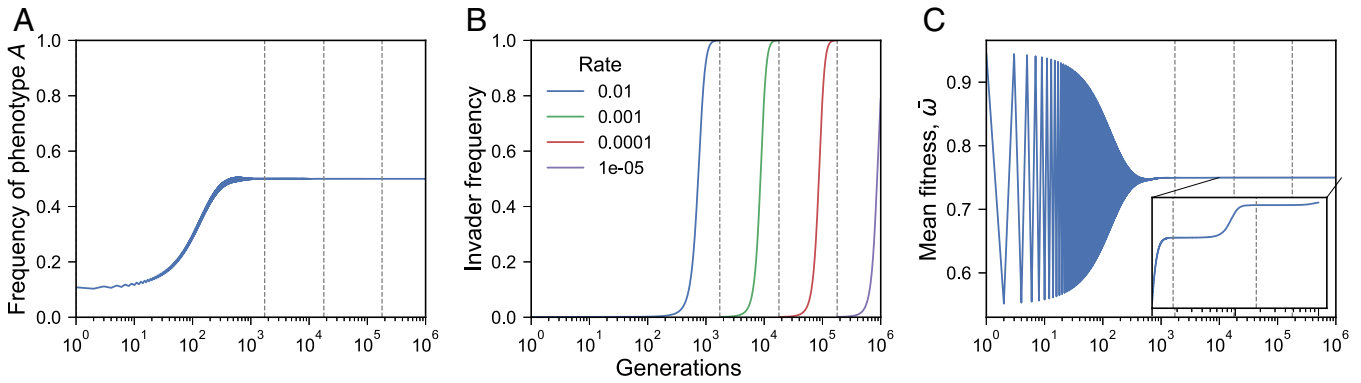

Fig. 4. Consecutive fixation of modifiers that reduce the vertical transmission rate in selection regime *A1B1*. The figure shows results of numerical simulations of evolution with two modifier alleles (Eq. **32**). When a modifier allele fixes (frequency $> 99.9\%$), a new modifier allele is introduced with a vertical transmission rate one order of magnitude lower (vertical dashed lines). (*A*) The frequency of phenotype *A* in the population over time. (*B*) The frequency of the invading modifier allele over time. (*C*) The population geometric mean fitness over time; *Inset* zooms in to show that the mean fitness increases slightly with each invasion. Invading alleles are introduced at frequency 0.01%; whenever their frequency drops below 0.01%, they are reintroduced. Parameters: vertical transmission rate of the initial resident modifier allele, $\rho_0 = 0.1$; fitness values: $W = 1$ and $w = 0.5$. The *x* axis is on a log scale, as each sequential invasion takes an order of magnitude longer to complete. Fig. S12 shows $w = 0.1$ and 0.9.

The external stability of $\underline{x}^*$ to the introduction of the modifier allele M with rate P is determined by the linear approximation matrix $\mathbf{L}$. We prove the following result in *SI Text*.

Result 8. $\mathbf{L}$ *has two positive eigenvalues, and*

i) *when* $P > \rho$, *the two eigenvalues are less than one;*
ii) *when* $P < \rho$, *the largest eigenvalue is larger than one; and*
iii) *when* $P = \rho$, *the largest eigenvalue is one.*

We conclude that, in the $A1B1$ selection regime, an allele m producing vertical transmission rate ρ is stable to the introduction of a modifier allele M with associated rate P if $P > \rho$, and it is unstable if $P < \rho$. Thus, in this case, evolution tends to reduce vertical transmission and hence, increase the rate of oblique transmission, and there is a reduction principle for the rate of vertical transmission (27, 32). The evolutionary dynamics of the reduction in ρ under the $A1B1$ cycling regime are shown in Fig. 4, which also illustrates the change in phenotype frequencies over time.

In the case of identically distributed random fitnesses w_A and w_B, Fig. 5 shows an example of the success of modifiers that reduce ρ. We have not, however, been able to prove that there is a reduction principle for this class of fluctuating fitnesses.

Values of the evolutionarily stable vertical transmission rate, ρ^*, for some $AkBl$ examples (*SI Text* and Fig. S10 have analytical details) are recorded in Table 1 for different values of w relative to $W = 1$. Interestingly, with $w = 0.1$, the evolutionarily stable value of ρ is zero for the $A1B2$ regime but not for the $A3B10$ and $A5B30$ regimes, in which the only stable values are those that lead to fixation of phenotype B (e.g., $\rho > 0.4625$ and $\rho > 0.1489$, respectively); these are, therefore, neutrally stable (Fig. S10). $AkBk$ results are plotted in Fig. 6*B*. In the $A2B2$ regime, $\rho^* = 0$, and there is reduction of vertical transmission for all selection values tested. However, for $AkBk$ regimes with $k > 2$, we find $\rho^* \neq 0$, and depending on w, ρ^* can be as high as 0.95. In Table 1, blank values for ρ^* indicate that our method was numerically unstable and that a precise value for ρ^* could not be obtained. This is why, in Fig. 6*B*, no ρ^* points are shown for $AkBk$ with $k > 19$. In Table 1, the word "fixation" indicates that fixation of B occurs, at which point there can be no effect of modification of ρ; ρ^* cannot be calculated in such cases.

Geometric Mean Fitness and Rate of Vertical Transmission

Under fluctuating selection, the geometric mean fitness of genotypes has been shown to determine their evolutionary dynamics (8, 30, 33). For the evolution of mutation rates that are controlled by genetic modifiers, the stable mutation rate and the mutation rate that maximizes the geometric mean fitness of the population seem to be the same when the period of environmental fluctuation is low enough (24). We can ask the same question here: is the stable rate ρ^* the same as the rate $\hat{\rho}$ that maximizes the

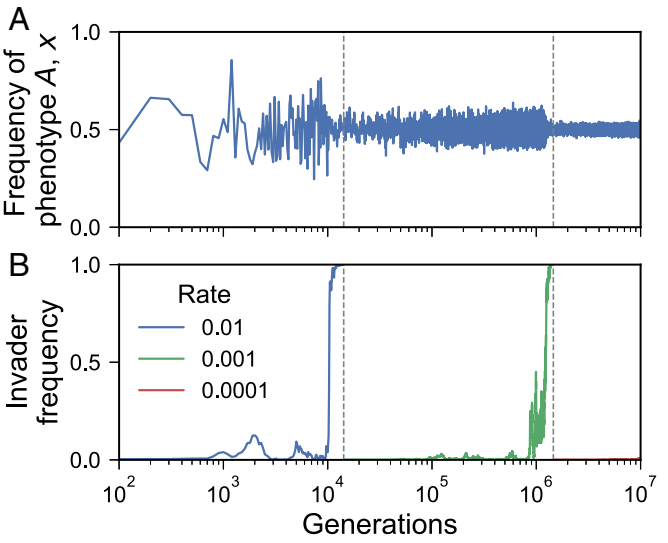

Fig. 5. Consecutive fixation of modifiers that reduce the vertical transmission rate ρ under symmetric randomly changing selection. The figure shows results of numerical simulations of evolution with two modifier alleles (Eq. **32**). When a modifier allele fixes (frequency $> 99.9\%$), a new modifier allele is introduced with a vertical transmission rate one order of magnitude lower (vertical dashed lines). (*A*) The frequency of phenotype *A* in the population over time. (*B*) The frequency of the invading modifier allele over time. Invading alleles are introduced at frequency 0.01%; whenever their frequency drops below 0.01%, they are reintroduced. Parameters: vertical transmission rate of the initial resident modifier allele is $\rho_0 = 0.1$, and the ratio of fitness values is $w_A/w_B = 10$ with probability 0.5 and $w_A/w_B = 0.1$ also with probability 0.5. The *x* axis is on a log scale, as each sequential invasion takes an order of magnitude longer to complete.

Table 1. Values of ρ^* (stable ρ) and $\hat{\rho}$ (optimal ρ)

k	l	$\{w\}^\dagger$	ρ^*	$\hat{\rho}$
1	1	0.1	0.000000	0.000000
1	1	0.5	0.000000	0.000000
1	1	0.9	0.000000	0.000000
1	2	0.1	0.000000	0.00065
1	2	0.5	Fixation	Fixation
1	2	0.9	Fixation	Fixation
2	2	0.1	0.000000	0.000000
2	2	0.5	0.000000	0.000000
2	2	0.9	0.000000	0.000000
3	10	0.1	>0.4265	0.00031
3	10	0.5	Fixation	Fixation
3	10	0.9	Fixation	Fixation
5	30	0.1	>0.1489	0.00027
5	30	0.5	Fixation	Fixation
5	30	0.9	Fixation	Fixation
12	12	0.1	0.84924	0.24347
12	12	0.5	0.91209	0.000000
12	12	0.9	0.95686	0.000000
20	20	0.1		0.223925
20	20	0.5	0.94643	0.000000
20	20	0.9	0.98304	0.000000
30	30	0.1		0.193280
30	30	0.5	0.96331	0.000000
30	30	0.9	0.99136	0.000000
50	50	0.1		0.15419
50	50	0.5	0.9768	0.22107
50	50	0.9	0.99581	0.000000

ρ^* is the uninvadable value of the vertical transmission rate. $\hat{\rho}$ is the rate that maximizes the geometric mean fitness at the stable equilibrium of the *AkBl* cycle.
†Note that $W = 1$.

equilibrium value of the geometric mean fitness under fluctuating selection? For the $A1B1$ selection regime, we have the following result.

Result 9. *If $W > w$ and $0 \le \rho \le 1$, then the mean fitness at the stable equilibrium in the $A1B1$ environment is a decreasing function of ρ.*

Proof: In $A1B1$, the stable frequency of phenotype A is, by Eq. **35**,

$$x^* = \frac{1}{2} - \frac{W + w - Z}{2(2-\rho)(W-w)}, \qquad [37]$$

where $Z = \sqrt{(1-\rho)^2(W-w)^2 + 4Ww} > 0$. The geometric mean fitness at the stable equilibrium is $\overline{w}^* \cdot \overline{w}^{**}$, where $\overline{w}^{**}$ is the mean fitness at the middle of the $A1B1$ cycle; in this case $\overline{w}^* = \overline{w}^{**}$ due to the symmetry between the two phenotypes A and B, which allows us to reduce the problem to properties of $\overline{w}^*$. Now, because $W > w$, $\overline{w}^*$ is an increasing linear function of x^*:

$$\overline{w}^* = x^* W + (1 - x^*)w = x^*(W - w) + w. \qquad [38]$$

Thus, $\overline{w}^*$ is decreasing in ρ if $dx^*/d\rho$ is negative. Using Eq. **37**,

$$\frac{dx^*}{d\rho} = -\frac{(1-\rho)(W-w)}{2(2-\rho)Z} - \frac{W + w - Z}{2(2-\rho)(W-w)} = \frac{x^* - \frac{1}{2}}{2-\rho} - \frac{(1-\rho)(W-w)}{2(2-\rho)Z}. \qquad [39]$$

From Eq. **36**, $0 < x^* \le \frac{1}{2}$, and therefore, $dx^*/d\rho < 0$, which completes the proof.

Fig. 4 illustrates the increase over time of the geometric mean fitness with decreasing ρ at a polymorphic equilibrium in the $A1B1$ regime. The values of $\hat{\rho}$ and ρ^* are the same in $A1B1$ and $A2B2$ regimes, namely both are zero. Fig. 1*B* shows the geometric mean fitness in the $A1B2$ regime, and we see that, for small values of w, this mean fitness increases as ρ decreases. At $w = 0.1$, Table 1 shows that $\hat{\rho}$ and ρ^* are roughly zero. In all $AkBk$ regimes that we tested with $w = 0.9$, the value of $\hat{\rho}$ was also zero, substantially different from the values of ρ^*, as shown in Fig. 6. Also in Fig. 6*A*, we see that, with $w = 0.1$, $\hat{\rho}$ changes from zero to positive in the $AkBk$ regimes with $k \ge 12$, while with $w = 0.5$, the change occurs at $k = 31$. In Fig. 6, with $w = 0.1$, $\hat{\rho}$ is between 0.15 and 0.24 for $12 \le k \le 50$, while with $w = 0.5$, $\hat{\rho}$ exceeds 0.2 for $31 \le k \le 50$. More details on the mismatch between ρ^*, which cannot be invaded, and $\hat{\rho}$, which maximizes geometric mean fitness, are given in Table 1, Figs. S7 and S8, and *SI Text*.

Finite Population Size

To include the effect of random drift due to finite population size in the above deterministic model, we use the Wright–Fisher model. Let X_t denote the number of individuals with phenotype A in a population of fixed size N at the tth generation, and suppose that $X_t = Nx$. Also, let x' represent the frequency of the phenotype A in the infinite population model in the next generation, namely (Eq. **2**)

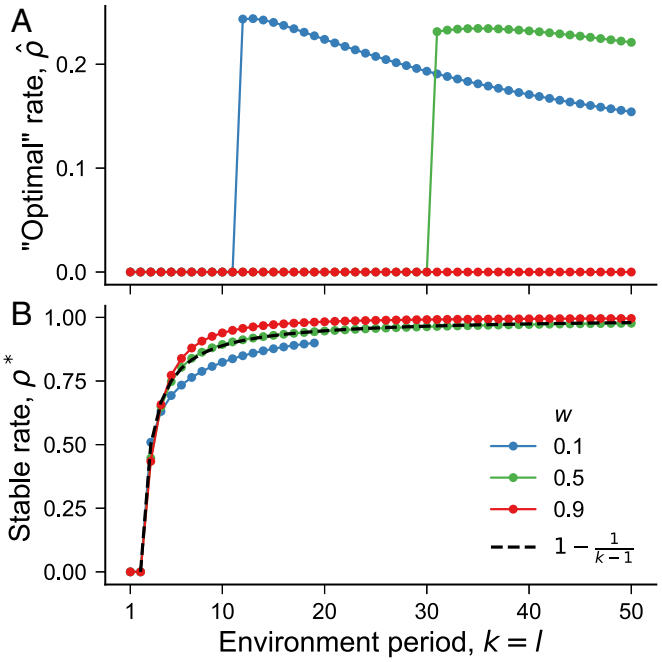

Fig. 6. Fitness "optimal" and evolutionary stable vertical transmission rate in *AkBk* selection regime. (*A*) The vertical transmission rate $\hat{\rho}$ that maximized the geometric average of the population mean fitness is zero (complete oblique transmission) when selection cycles quickly between favoring phenotype *A* and *B* and then abruptly transitions to ≈ 0.2 followed by a slow decrease (Figs. S5 and S6 have details on the abrupt transition). (*B*) The evolutionary stable rate ρ^*, which cannot be invaded by modifiers with either higher or lower vertical transmission rate *P*, rapidly increases from zero when selection cycles are short ($k = 1$ or 2) to roughly one when selection cycles are longer. The dashed line shows $1 - \frac{1}{k-1}$, which fits the values for $w = 0.5$ (41). The values for $w = 0.1$ (blue) could not be calculated for $k > 19$ due to numerical instability when selection is strong and the duration between selection fluctuations is long. In all cases, $W = 1$. *SI Text* has details on how we calculated the stable rate.

$$x' = \rho \frac{w_A}{\overline{w}} x + (1-\rho)x. \quad [40]$$

Then, according to the Wright–Fisher model (34), X_{t+1}, the number of individuals of phenotype A at generation $(t+1)$, is determined by the probability

$$P\left(X_{t+1} = j \mid X_t = Nx\right) = \binom{N}{j} \left(x'\right)^j \left(1-x'\right)^{N-j} \quad [41]$$

for $j = 0, 1, 2, \ldots, N$. Thus, the fluctuations in the numbers of phenotypes A and B in the population of size N are generated by the Wright–Fisher Markov chain, where, given that $X_t = Nx$, X_{t+1} has a binomial distribution with parameters (N, x').

This Markov chain has two absorbing states, $X_t = N$ and $X_t = 0$, corresponding to the two fixations in A and B, respectively, and we are interested in the fixation probabilities and the time to fixation of these two absorbing states as functions of the initial frequency x and also of ρ, w_A, and w_B. To these ends, we use a diffusion approximation to the process $\{X_t\}$, which allows us to compute $u(x)$, the probability that phenotype A goes to fixation when its initial frequency is x, namely

$$u(x) = \frac{1 - e^{-2\rho s x}}{1 - e^{-2\rho s}}. \quad [42]$$

The expected time to fixation in A starting from an initial frequency of x is given by

$$T(x) = \frac{1-u(x)}{\rho s} \int_0^x \frac{e^{2\rho s \xi} - 1}{\xi(1-\xi)} d\xi + \frac{u(x)}{\rho s} \int_x^1 \frac{1 - e^{-2\rho s(1-\xi)}}{\xi(1-\xi)} d\xi, \quad [43]$$

where $u(x)$ is given in Eq. **42**, and in generations, $T(x)$ is multiplied by N (the derivation is in *SI Text*). Unfortunately, the integrals in Eq. **43** cannot be done in closed form unless $\rho s = 0$, in which case $u(x) = x$ and $T(x) = -2x \ln x - 2(1-x)\ln(1-x)$ (ref. 34, p. 160), and only numerical computation of $T(x)$ is possible for specified values of x, ρ, and s.

For the fixation probability $u(x)$, we have the following result.

Result 10. *When $s > 0$, so that the phenotype A is favored, the fixation probability $u(x)$ is monotone increasing in ρ.*

The proof of *Result 10* is in *SI Text*. Fig. S9 compares the fixation probability and time to fixation derived numerically from simulating the Wright–Fisher Markov chain with the diffusion-derived values of $u(x)$ and $T(x)$. The fit is seen to be very good. Note that, when N is large, the Wright–Fisher model exhibits persistent fluctuation around the deterministic expectation, as shown by the orange traces in Fig. S2.

We can also develop a diffusion approximation for the case of a cycling environment. Suppose that selection changes in cycles of length n, such that, within the cycle, the fitness parameters are w_A^t, w_B^t for $t = 1, 2, \ldots, n$. Also, let

$$\frac{1}{N} s_t \simeq w_A^t - w_B^t, \qquad S_t = \sum_{i=1}^{t} s_i, \qquad t = 1, 2, \ldots, n. \quad [44]$$

Following Karlin and Levikson (35), we have the following result.

Result 11. *The mean $\mu(x)$ and variance $\sigma^2(x)$ of the change in the frequency of A in one generation for the diffusion approximation in the case of a cycling environment $AkBl$, where $k + l = n$, are*

$$\mu(x) = \rho S_n x(1-x)$$
$$\sigma^2(x) = nx(1-x). \quad [45]$$

The proof of Result 11, based on induction on n, is given in SI Text.

Using the moments in Eq. **45**, the fixation probability $u(x)$ and the expected time $T(x)$ to fixation from an initial frequency of x can be computed, where s is replaced by s_n/n. We find

$$u(x) = \frac{1 - e^{-2\rho \frac{S_n}{n} x}}{1 - e^{-2\rho \frac{S_n}{n}}}, \quad [46]$$

and $T(x)$ can be computed similarly.

In the case of the $AkBl$ cycling environment, we write $n = k + l$, and if $w_A = W$, $w_B = w$ for k generations and $w_A = w$, $w_B = W$ for l generations, we have

$$S_n = S_{k+l} = N(k-l)(W-w). \quad [47]$$

Fig. 7 shows an example of how $(k-l)$, ρ, and $(W-w)$ in Eq. **46** for $u(x)$ interact to affect fixation probabilities. More examples are illustrated in Fig. S11.

Discussion

Nonchromosomal modes of phenotypic transmission are receiving increasing attention (36–38), especially with respect to their potential role in adaptation and maintenance of diversity (39). Here, we have focused on a dichotomous phenotype transmitted through a combination of parental and nonparental transmission. In addition to the roles that these transmission modes play in the dynamics of phenotypic diversity in large and small populations, we have also investigated a genetic model for the evolution of the transmission mode itself.

Our model differs markedly from that of Xue and Leibler (26), who took the individual phenotypic distribution (i.e., the probability that an individual develops one of a set of phenotypes) to be the inherited trait. In our model, the transmitted trait is the phenotype itself. Thus, with two phenotypic states A and B, we track the frequency x of A, whereas Xue and Leibler (26) focus on the dynamics of the per-individual probability π_A of learning the phenotype A. One interpretation of our model is as a mean

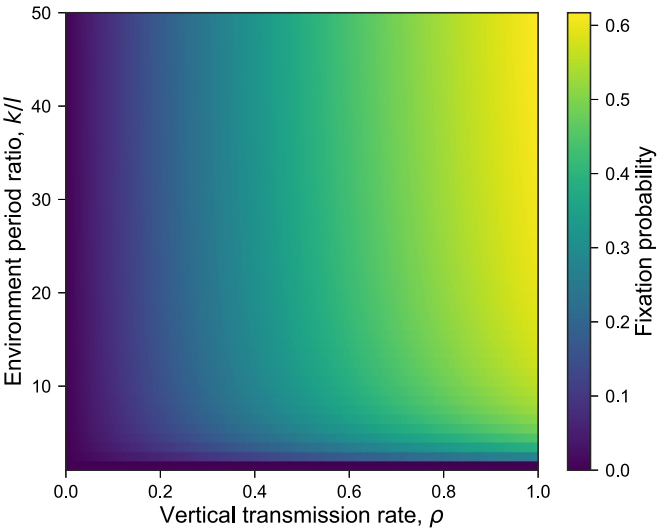

Fig. 7. Fixation in a finite population with different ratios of selection periods $\frac{k}{l}$. Fixation probability of phenotype A when starting with a single copy in a population of size N: $u(1/N) = (1 - \exp(-2\rho\frac{k-l}{k+l}(W-w))/(1 - \exp(-2N\rho\frac{k-l}{k+l}(W-w))$ (Eqs. **46** and **47**). k and l are the numbers of generations in which phenotypes A and B, respectively, are favored by selection. Here, fitness of the favored phenotype is $W = 1$, fitness of the disfavored phenotype is $w = 0.5$, and the population size is $N = 10,000$. Fig. S11 shows additional examples.

value approximation to the model of Xue and Leibler (26), where x, the state in our model, is the average of the population distribution of individual phenotype probabilities.

In a constant environment, the higher the vertical transmission rate ρ, the faster the approach to fixation of the favored phenotype: A if $w_A > w_B$ or B if $w_B > w_A$. Here, $1-\rho$, the oblique transmission rate, represents the added chance that an offspring becomes A by learning from the parent's population after learning from the parents who have undergone selection (Eq. **2**). This simple phenotypic model does not allow a polymorphism to be achieved in a constant environment, but with more oblique transmission, approach to fixation is retarded.

With fluctuating environments, the dynamics of the phenotype frequencies are, in general, much more complicated. In particular, with deterministically cycling symmetric fitness values (the $AkBl$ model), it is impossible for fixation in A and B to both be stable. If $k = l$, for example, neither fixation is stable, and there is a single stable polymorphic equilibrium (with phenotypes A and B present) (*Result 5*). In the $A1B1$ case, this polymorphism is globally stable. In the $AkBl$ case, bounds on l/k that determine the instability of both fixations and hence, the protection of polymorphism are given by the inequalities of Eq. **20**, which depend on both the fitness differences and the rate ρ of vertical transmission. We conjecture that, with $k \neq l$, there is a unique stable polymorphism if both fixations are unstable. This result is similar to the storage effect (40), in which protection from selection maintains species coexistence: consider two species, A and B, with overlapping generations, an equal death rate ρ, and different growth rates w_A and w_B; then, Eq. **2** describes the change in frequency of species A. In our model, oblique transmission can be said to protect the disfavored phenotype from selection, because it allows transmission without reproduction.

In deterministic one-locus, two-allele diploid population genetic models with cycling fitness regimes, Haldane and Jayakar (33) first showed the relevance of the geometric mean of genotypic fitness (compare Eqs. **16** and **17**) for the maintenance (or loss) of polymorphism. However, with equal homozygote fitness, alternating in strength as a two-generation cycle (compare with $A1B1$), Karlin and Liberman (31) extended the results of Haldane and Jayakar (33) and found conditions under which both allelic fixations and polymorphic equilibrium could all be stable, with the evolution depending on initial allele frequencies as well as the homozygote fitness differences between alternate generations. Our haploid model does not seem to produce such dependence on the initial conditions.

When the fitnesses w_A and w_B are treated as random variables rather than varying cyclically, stochastic local stability is the appropriate analog to local stability in the case of cyclic fitness variation. While fixations in phenotypes A and B cannot both be stochastically stable in this case, both may be unstable, and a polymorphic distribution may result. The variance of this distribution is greater for larger values of ρ. This is because the stochastic local stability conditions involve $E\{\log[1-\rho+\rho(w_A/w_B)]\}$, and the effect of the variance of (w_A/w_B) will clearly increase as ρ increases. In the finite population case, a greater level of vertical transmission makes selection more effective, increasing the probability $u(x)$ of fixation and reducing the expected time to fixation.

We have shown that, in the $A1B1$ case, the rate of vertical transmission tends to decrease when it is under the control of a genetic modifier. From numerical iteration, it seems that this is also true in the random selection case when the fitnesses of A and B are identically distributed and independent between generations. However, for $AkBl$ selection regimes more complicated than $A1B1$, evolution of a modifier of vertical transmission is not straightforward. While reduction of ρ occurs in the $A2B2$ regime, the uninvadable value ρ^* is not zero for all of the fitness values explored in $AkBk$ regimes with $k > 2$ (Fig. 6*B* and Table 1). In fact, ρ^* increases sharply as k increases beyond $k = 2$. This is an unusual scenario for genetic modifiers, although it must be noted that a modifier of ρ is not neutral; it affects primary selection, while neutral modifiers of recombination, mutation, and migration affect induced or secondary selection.

The dependence of the modifier dynamics on the strength of selection (that is, w when $W = 1$) is complicated by the approach of the system to fixation. When the phenotype frequencies become exceedingly small, dependence of the dynamics of the modifier of ρ becomes extremely difficult to detect due to numerical instability; this is especially true for larger values of k in $AkBk$ regimes when w is small (Fig. 6*B* and Table 1) (with $k \geq 19$).

Fig. 6*A* (Table 1) shows that the value $\hat{\rho}$ that maximizes the geometric mean fitness is the same as the evolutionarily stable value ρ^* in the $A1B1$ and $A2B2$ selection regimes. For $AkBk$ regimes with $k > 2$, our numerical analysis shows that $\hat{\rho}$ depends strongly on the strength of selection (i.e., the value of w relative to $W = 1$). For $AkBl$ regimes with $w = 0.1$, the difference between $\hat{\rho}$ and ρ^* is seen even with the $A1B2$ environment. For $AkBk$ regimes and $w = 0.9$, we find $\hat{\rho} = 0$, while ρ^* is close to 0.9. For larger values of k, $\hat{\rho}$ is between 0.15 and 0.25, while ρ^* remains above 0.8 and can reach 0.99 for very large k. Comparing Fig. 6*A* with the asymptotic growth rate (AGR) of Xue and Leibler (26), whose parameter η is the rate at which an individual learns from its parental lineage, there is a similarity of our curves for $w = 0.1$ and 0.5 with their curve in the $AkBk$ environment. They show the AGR decreasing with η in the $AkBk$ regime for small k, but larger values of k entail that the AGR has a maximum for an intermediate value of η.

Although the models of Xue and Leibler (26) and that analyzed here both incorporate parental and nonparental transmission, they do so in qualitatively different ways. The model treated in this paper is squarely in the tradition of gene–culture coevolutionary theory together with modifier theory from population genetics. The different findings from the two classes of models are interesting and suggest that additional exploration of the overlaps and discrepancies between the two approaches would be worthwhile.

ACKNOWLEDGMENTS. This research was supported, in part, by the Stanford Center for Computational, Evolutionary and Human Genomics.

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Supporting Information

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SI Text

Proof of Uniqueness in *Result 5*. Following Eq. **10**, the transformation of the frequency x of phenotype A is

$$x' = F(x) = \underbrace{F_B \circ \cdots \circ F_B}_{l \text{ times}} \circ \underbrace{F_A \circ \cdots \circ F_A}_{k \text{ times}}(x). \quad \textbf{[S1]}$$

Using Eqs. **25** and **26**, we can write

$$F'_A(x) = \rho \frac{wW}{\left[\overline{w}(x)\right]^2} + (1-\rho), \quad \overline{w}(x) = (W-w)x + w \quad \textbf{[S2]}$$

$$F'_B(x) = \rho \frac{wW}{\left[\widetilde{w}(x)\right]^2} + (1-\rho), \quad \widetilde{w}(x) = (w-W)x + W. \quad \textbf{[S3]}$$

Since $F'_A(x) > 0$, $F'_B(x) > 0$ for $0 \le x \le 1$, all of the functions F_A, F_B, $F_A \circ \cdots \circ F_A$, $F_B \circ \cdots \circ F_B$, and F are monotone increasing for $0 \le x \le 1$.

From *Result 2*, the two fixations $x = 0$ and $x = 1$ are not stable, because $F'(0) > 1$ and $F'(1) > 1$. Therefore,

$$F(x) - x > 0 \text{ for } x > 0 \text{ "near" } x = 0, \quad \textbf{[S4]}$$

$$F(x) - x < 0 \text{ for } x < 1 \text{ "near" } x = 1. \quad \textbf{[S5]}$$

Hence, as $F(x) - x$ is a continuous function of x for $0 \le x \le 1$, there exists (at least one) polymorphic equilibrium x^* with $0 < x^* < 1$, such that $F(x^*) = x^*$.

If there is more than one polymorphic equilibrium, and as there is a finite number of equilibria, let x^* be the "closest" polymorphic equilibrium to $x = 0$. Since $F(x) > x$ for $0 < x < x^*$, $F(x) < x$ for $x > x^*$ (at least "near" x^*), and $F(x)$ is a monotone increasing function in $[0, 1]$, x^* must be locally stable.

Let $\hat{x} = F(\hat{x})$ with $0 < \hat{x} < 1$ be any polymorphic equilibrium; then, from **[S1]**, its evolution in the $k + k$ generations is

$$\hat{x} = \hat{x}_0 \overset{A}{\to} \hat{x}_1 \overset{A}{\to} \cdots \overset{A}{\to} x_{k-1} \overset{B}{\to} \hat{y}_0 \overset{B}{\to} \hat{y}_1 \overset{B}{\to} \cdots \overset{B}{\to} \hat{y}_{k-1} \overset{A}{\to} \hat{x}_0 = \hat{x}. \quad \textbf{[S6]}$$

Due to the symmetry between phenotypes A and B, we have

$$\hat{y}_t = 1 - \hat{x}_t, \qquad \overline{w}(\hat{x}_t) = \widetilde{w}(\hat{y}_t) \quad \textbf{[S7]}$$

for all $t = 0, 1, 2, \ldots, k-1$.

The polymorphic equilibrium $\hat{x}$ is locally stable if $F'(\hat{x}) < 1$ or from **[S1–S3]**, if

$$\prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\overline{w}(\hat{x}_t)\right]^2} + (1-\rho) \right\} \cdot \prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\widetilde{w}(\hat{y}_t)\right]^2} + (1-\rho) \right\} < 1. \quad \textbf{[S8]}$$

Applying **[S7]**, we conclude that $\hat{x}$ is locally stable if

$$\prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\overline{w}(\hat{x}_t)\right]^2} + (1-\rho) \right\} < 1. \quad \textbf{[S9]}$$

As x^*, the closest polymorphic equilibrium to $x = 0$, is stable, then **[S9]** implies that

$$\prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\overline{w}(x_t^*)\right]^2} + (1-\rho) \right\} \le 1, \quad \textbf{[S10]}$$

where x_t^* for $t = 0, 1, \ldots, k-1$ is defined as in **[S6]**.

If $\hat{x}$ is any polymorphic equilibrium other than x^*, then $\hat{x} > x^*$ or $\hat{x}_0 > x_0^*$ by **[S4]**. Since F_A is a monotone increasing function and

$$\hat{x}_{t+1} = F_A(\hat{x}_t), \quad x_{t+1}^* = F_A(x_t^*) \quad t = 0, 1, \ldots, k-1, \quad \textbf{[S11]}$$

then by induction, we have $\hat{x}_t > x_t^*$ for all $t = 0, 1, 2, \ldots, k-1$. In addition, as $\overline{w}(x) = (W-w)x + w$ and $W > w$, we also have $\overline{w}(\hat{x}_t) > \overline{w}(x_t^*)$ for all $t = 0, 1, 2, \ldots, k-1$ and

$$\prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\overline{w}(\hat{x}_t)\right]^2} + (1-\rho) \right\} < \prod_{t=0}^{k-1} \left\{ \rho \frac{wW}{\left[\overline{w}(x_t^*)\right]^2} + (1-\rho) \right\} \le 1. \quad \textbf{[S12]}$$

Hence, $\hat{x}$ is also locally stable. However, it is impossible that all polymorphic equilibria are stable unless there is only one stable polymorphic equilibrium. Therefore, x^* is the unique stable polymorphic equilibrium, and since $F(x) > x$ for $0 < x < x^*$, $F(x) < x$ for $x^* < x < 1$, and $F(x)$ is monotone increasing in $[0, 1]$, therefore, x^* is globally stable.

Proof of *Result 6*. Rewrite recursion Eq. **28** as

$$\frac{x_t + 1}{x_t} = (1 + \rho s_t)\left[1 - x_t \frac{\rho s_t(1 + s_t)}{(1 + \rho s_t)(1 + x_t s_t)}\right]. \quad \textbf{[S13]}$$

Then,

$$\log x_{t+1} - \log x_t = \log(1 + \rho s_t) + \log\left[1 - x_t \frac{\rho s_t(1 + s_t)}{(1 + \rho s_t)(1 + x_t s_t)}\right]. \quad \textbf{[S14]}$$

Summation yields

$$\frac{1}{t}\left[\log x_t - \log x_0\right] = \frac{1}{t}\sum_{n=0}^{t-1} \log(1 + \rho s_n) + \frac{1}{t}\sum_{n=0}^{t-1} \log\left[1 - x_n \frac{\rho s_n(1 + s_n)}{(1 + \rho s_n)(1 + x_n s_n)}\right]. \quad \textbf{[S15]}$$

Let $\mu = E\left[\log(1 + \rho s_t)\right]$. As $\{s_t\}_{t\geq 0}$ are independent and identically distributed random variables, the strong law of large numbers applies, and

$$\lim_{t\to\infty} \frac{1}{t}\sum_{n=0}^{t-1} \log(1 + \rho s_n) = \mu \quad \textbf{[S16]}$$

almost surely.

Let ζ be such that $\frac{1}{t}\sum_{n=0}^{t-1} \log[1 + \rho s_n(\zeta)] = \mu$, and assume that $\lim_{t\to\infty} x_t(\zeta) = 0$. As the random variables $\{s_t\}_{t\geq 0}$ are uniformly bounded,

$$x_t(\zeta)\frac{\rho s_t(\zeta)[1 + s_t(\zeta)]}{[1 + \rho s_t(\zeta)][1 + x_t(\zeta)s_t(\zeta)]} \;\; t \to \infty \; 0 \quad \textbf{[S17]}$$

and

$$\lim_{t\to\infty} \frac{1}{t}\sum_{n=0}^{t-1} \log\left[1 - x_n(\zeta)\frac{\rho x_n(\zeta)[1 + s_n(\zeta)]}{[1 + \rho s_n(\zeta)][1 + x_t(\zeta)s_n(\zeta)]}\right] = 0. \quad \textbf{[S18]}$$

Thus, **[S15]** implies that

$$\lim_{t\to\infty} \frac{1}{t}\left[\log x_t(\zeta) - \log x_0(\zeta)\right] = \mu. \quad \textbf{[S19]}$$

If $\mu = E\left[\log(1 + s_t)\right] > 0$, then from **[S19]**, we deduce that $\lim_{t\to\infty} x_t(\zeta) = \infty$, a contradiction. Therefore, when $\mu > 0$, $P(\lim_{t\to\infty} x_t = 0) = 0$, and fixation of B ($x^* = 0$) is stochastically locally unstable.

Thus, by *Result 6*, for $x^* = 0$ to be stochastically locally stable, it is necessary that $E[\log(1 + \rho s_t)] \leq 0$. In fact, the strict inequality is sufficient.

Fig. 3 presents a numerical example of the dynamics of recursion Eq. **28** with a specific random selection coefficient s_t.

Proof of *Result 7*. Let $\mu = E[\log(1 + \rho s_t)]$. Then, as $\{s_t\}_{t\geq 0}$ are independent and identically distributed random variables, the strong law of large number applies and almost surely

$$\lim_{t\to\infty} \frac{1}{t}\sum_{n=0}^{t-1} \log(1 + \rho s_n) = \mu < 0. \quad \textbf{[S20]}$$

Appealing to the Egoroff Theorem, for any $\epsilon > 0$, there exists T, such that

$$P\left(\frac{1}{t}\sum_{n=0}^{t-1} \log(1 + \rho s_n) < \frac{\mu}{2} \text{ for all } t \geq T\right) \geq 1 - \epsilon. \quad \textbf{[S21]}$$

As $0 \leq \rho \leq 1$ and the $\{s_t\}_{t\geq 0}$ are uniformly bounded, we can find a $\delta' > 0$, such that

$$x_t < \delta' \Longrightarrow \left|\log\left[1 - x_t \frac{\rho s_t(1 + s_t)}{(1 + \rho s_t)(1 + x_t s_t)}\right]\right| < -\frac{\mu}{4}. \quad \textbf{[S22]}$$

Also, as $0 \leq x_t \leq 1$ for all t,

$$x_{t+1} = x_t \frac{1 + \rho s_t + x_t(1 - \rho)s_t}{1 + x_t s_t} < K x_t, \quad \textbf{[S23]}$$

where K is independent of t. It follows that there exists a δ with $0 < \delta < \delta'$, such that

$$x_o < \delta \Longrightarrow x_t < \delta' \text{ for all } t = 0, 1, 2, \ldots, T - 1. \quad \textbf{[S24]}$$

Let ξ be a realization of the evolutionary process, such that

$$\frac{1}{t}\sum_{n=0}^{t-1}\log[1+\rho s_n(\xi)] < \frac{\mu}{2} \text{ for all } t \geq T, \qquad \textbf{[S25]}$$

and assume that $x_0 < \delta$. Then,

$$\begin{aligned}&\frac{1}{T}[\log x_T(\xi) - \log x_0(\xi)] = \\ &\frac{1}{T}\sum_{n=0}^{T-1}\log[1+\rho s_n(\xi)] + \frac{1}{T}\sum_{n=0}^{T-1}\log[1 - x_n(\xi)\frac{\rho s_n(\xi)[1+s_n(\xi)]}{[1+\rho s_n(\xi)][1+x_n(\xi)s_n(\xi)]}] \\ &< \frac{\mu}{2} - \frac{\mu}{4} = \frac{\mu}{4} < 0, \end{aligned} \qquad \textbf{[S26]}$$

and therefore, $x_T(\xi) < x_0(\xi) < \delta'$. Invoking induction, we get that, for $t \geq T$,

$$\frac{1}{t}\log\frac{x_t(\xi)}{x_0} \leq \frac{\mu}{4}, \qquad \textbf{[S27]}$$

or for all $t \geq T$,

$$x_t(\xi) \leq x_0 \exp\left(\frac{\mu}{4}t\right). \qquad \textbf{[S28]}$$

As $\mu < 0$, this implies that $x_t(\xi)\ t \to \infty\, 0$. Therefore, we have shown that, for given $\epsilon > 0$, there is a $\delta > 0$, such that, if $0 < x_0 < \delta$, then $P\left(\lim_{t\to\infty} x_t = 0\right) \geq 1 - \epsilon$; therefore, $x^* = 0$, and the fixation in B is stochastically locally stable. The second statement of *Result 6* follows from the convexity of the log function and Jensen's inequality.

Proof of *Result 8*. The external stability of $\underline{x}^*$ (Eqs. **35** and **36**) to the introduction of the modifier allele M with rate P is determined by the linear approximation matrix $\mathbf{L} = \mathbf{L}_2 \cdot \mathbf{L}_1$ near x^*, which is derived from Eq. **32** and given by

$$\overline{w}^*\mathbf{L}_1 = \begin{bmatrix} W\left[(1-P)x_1^* + P\right] & w(1-P)x_1^* \\ W(1-P)x_2^* & w\left[(1-P)x_2^* + P\right]\end{bmatrix} \qquad \textbf{[S29]}$$

and

$$\overline{w}^{**}\mathbf{L}_2 = \begin{bmatrix} w\left[(1-P)x_1^{**} + P\right] & W(1-P)x_1^{**} \\ w(1-P)x_2^{**} & W\left[(1-P)x_2^{**} + P\right]\end{bmatrix}, \qquad \textbf{[S30]}$$

where $\underline{x}^{**} = T_1\underline{x}^*$, $x_1^{**} = x_2^* = 1 - x_1^*$, $x_2^{**} = x_1^*$, and

$$\overline{w}^* = Wx_1^* + wx_2^*, \qquad \overline{w}^{**} = wx_1^{**} + Wx_2^{**}. \qquad \textbf{[S31]}$$

Due to the symmetry between the two phenotypes A and B in the $A1B1$ case, we have $x_1^{**} = x_2^*$ and $x_2^{**} = x_1^*$, so that $\overline{w}^{**} = \overline{w}^*$, and in fact,

$$\overline{w}^*\mathbf{L}_2 = \begin{bmatrix} w\left[(1-P)x_2^* + P\right] & W(1-P)x_2^* \\ w(1-P)x_1^* & W\left[(1-P)x_1^* + P\right]\end{bmatrix}. \qquad \textbf{[S32]}$$

Note that, as $\underline{x}^* = T_2(T_1\underline{x}^*)$ with $x_3^* = x_4^* = 0$, from **[S29]** and **[S30]** with $P = \rho$, we have

$$\begin{bmatrix} x_1^* \\ x_2^*\end{bmatrix} = \mathbf{L}_2 \cdot \mathbf{L}_1 \begin{bmatrix} x_1^* \\ x_2^*\end{bmatrix} = \mathbf{L}\begin{bmatrix} x_1^* \\ x_2^*\end{bmatrix}. \qquad \textbf{[S33]}$$

Hence, when $P = \rho$, one of the eigenvalues of $\mathbf{L}$ is one. In general, $\mathbf{L} = \mathbf{L}_2 \cdot \mathbf{L}_1$, and using **[S29]** and **[S32]**, we have

$$\begin{aligned}(\overline{w}^*)^2\,\mathbf{L}_{11} &= Ww\left[(1-P)^2x_1^*x_2^* + P\right] + \left[w(1-P)x_1^*\right]^2 \\ (\overline{w}^*)^2\,\mathbf{L}_{12} &= W(1-P)\left[P + x_1^*(1-P)\right]\left[Wx_2^* + wx_1^*\right] \\ (\overline{w}^*)^2\,\mathbf{L}_{21} &= w(1-P)\left[1 - x_1^*(1-P)\right]\left[Wx_2^* + wx_1^*\right] \\ (\overline{w}^*)^2\,\mathbf{L}_{22} &= Ww\left[(1-P)^2x_1^*x_2^* + P\right] + \left[W(1-P)x_2^*\right]^2.\end{aligned} \qquad \textbf{[S34]}$$

The external stability of $\underline{x}^*$ is determined by the eigenvalues of $\mathbf{L}$, namely the roots of its characteristic polynomial $R(\lambda) = \det(\mathbf{L} - \lambda I)$, with I the 2×2 identity matrix. From Eq. **S34**, $R(\lambda) = a_2\lambda^2 + a_1\lambda + a_0$, where

$$a_0 = \frac{P^2W^2w^2}{(\overline{w}^*)^4}, \quad a_1 = -\frac{2PWw + (1-P)^2[Wx_2^* + wx_1^*]^2}{(\overline{w}^*)^2}, \quad a_2 = 1. \qquad \textbf{[S35]}$$

As $\mathbf{L}$ is a positive matrix, by the Perron–Frobenius theorem, $\mathbf{L}$ has a positive eigenvalue, and as $a_0 > 0$ and $a_2 = 1$, the product of the two eigenvalues of $\mathbf{L}$ is positive. Thus, $\mathbf{L}$ has two positive eigenvalues. Let $R(1) = R(1;P)$; then, from **[S35]**,

$$R(1;P) = \frac{W^2w^2 - (\overline{w}^*\widetilde{w}^*)^2}{(\overline{w}^*)^4}P^2 + 2P\frac{(\widetilde{w}^*)^2 - Ww}{(\overline{w}^*)^2} + \frac{(\overline{w}^*)^2 - (\widetilde{w}^*)^2}{(\overline{w}^*)^2}, \qquad \textbf{[S36]}$$

where $\widetilde{w}^* = Wx_2^* + wx_1^*$.

By Eq. **36**, $\left(\sqrt{Ww}-w\right)/(W-w) < x_1^* < \frac{1}{2}$, from which it is easily seen that

$$\sqrt{Ww} < \overline{w}^* < \widetilde{w}^*. \qquad \textbf{[S37]}$$

When $P=\rho$, one of the eigenvalues of **L** is one; hence, $R(1;\rho)=0$. Another root of $R(1;P)=0$ is $\left[(\overline{w}^*)^2+\overline{w}^*\widetilde{w}^*\right]/\left[Ww+\overline{w}^*\widetilde{w}^*\right]$, which by Eq. **S37**, is larger than one. As $R(1;0)=\left[(\overline{w}^*)^2-(\widetilde{w}^*)^2\right]/(\overline{w}^*)^2<0$ by Eq. **S37**, we deduce that, when $0<P<\rho$, $R(1;P)<0$, whereas when $\rho<P<1$, $R(1;P)>0$. Hence, when $P<\rho$, $R(1)<0$, and since $a_2=1$, $R(+\infty)>0$; therefore, we conclude that $R(\lambda)=0$ has a positive root larger than one, and the largest positive eigenvalue of **L** is larger than one.

When $P>\rho$, we have $R(1)>0$ and also, $R(0)=a_0>0$. As $R(\lambda)=0$ has two positive roots and as $a_2>0$, $R(\lambda)$ is convex: either the two positive roots are less than one or both larger than one. However, the product of the two roots is $P^2W^2w^2/(\overline{w}^*)^2<1$ by Eq. **S37**; thus, when $P>\rho$, the two positive eigenvalues of **L** are less than one.

Proof of *Result 10*. Without loss of generality and for the ease of representation, we will show that, for $t>0$,

$$v(x;t)=\frac{1-e^{-tx}}{1-e^{-t}} \qquad \textbf{[S38]}$$

is monotone increasing as a function of t. Observe that

$$\frac{\partial v}{\partial t}=\frac{\left(1-e^{-t}\right)xe^{-tx}-\left(1-e^{-tx}\right)e^{-t}}{\left(1-e^{-t}\right)^2}. \qquad \textbf{[S39]}$$

For the monotonicity, we have to show that

$$f(x;t)=\left(1-e^{-t}\right)xe^{-tx}-\left(1-e^{-tx}\right)e^{-t}\geq 0 \qquad \textbf{[S40]}$$

when $t>0$ and $0\leq x\leq 1$. Note that $f(0;t)=0$ and $f(1;t)=0$. Also,

$$\frac{\partial f}{\partial x}=\left(1-e^{-t}\right)\left(e^{-tx}-txe^{-tx}\right)-te^{-tx}e^{-t} \qquad \textbf{[S41]}$$

or

$$\frac{\partial f}{\partial x}=e^{-tx}\left[\left(1-e^{-t}\right)(1-tx)-te^{-t}\right]=e^{-tx}g(x;t), \qquad \textbf{[S42]}$$

say where for fixed t, $g(x;t)$ is a linear function of x, which vanishes at $x_0=(1-e^{-t}-te^{-t})/t(1-e^{-t})$. If $t>0$, $e^t>1+t$; therefore, $1>e^{-t}(1+t)$ and $x_0>0$. Also, if $t>0$, $e^{-t}>1-t$, and therefore, $1-e^{-t}-te^{-t}<t(1-e^{-t})$ and $x_0<1$. Since $g(0,t)=1-e^{-t}-te^{-t}>0$ and $g(1;t)=(1-e^{-t})(1-t)-te^{-t}<0$ for $t>0$, we deduce that $\frac{\partial f}{\partial x}(x,t)>0$ for $0<x<x_0$ and $\frac{\partial f}{\partial x}(x,t)<0$ for $x_0<x<1$ for all $t>0$. These facts combined with $f(0,t)=f(1;t)=0$ prove that $f(x;t)\geq 0$ for $0\leq x\leq 1$ [in fact, $f(x;t)>0$ for $0<x<1$], and inequality **[S40]** is satisfied as desired.

Proof of *Result 11*. The proof is based on induction on n, where to prove Eq. **45**, we show that, if X_t is the number of individuals with phenotype A at stage t of the cycle and x is the initial frequency of A, then

$$E\left(\frac{X_t}{N}-x\right)\simeq\frac{1}{N}\rho S_t x(1-x), \qquad V\left(\frac{X_t}{N}\right)\simeq\frac{1}{N}tx(1-x), \qquad \textbf{[S43]}$$

where N is the size of the population. When $t=1$, **[S43]** coincides with the constant environment case. Assuming **[S43]**, we go to $t+1$. Now, X_{t+1} given $X_t=Ny$ has a binomial distribution with parameters (N,y'). Hence,

$$E\left(\frac{X_{t+1}}{N}-\frac{X_t}{N}\middle|\,X_t=Ny\right)=y'-y. \qquad \textbf{[S44]}$$

Following ref. 1, chap. 5, $y'-y\simeq(1/N)\rho s_{t+1}y(1-y)$, and therefore,

$$E\left(\frac{X_{t+1}}{N}-\frac{X_t}{N}\middle|\,X_t\right)\simeq\frac{1}{N}\rho s_{t+1}\frac{X_t}{N}\left(1-\frac{X_t}{N}\right). \qquad \textbf{[S45]}$$

Observe that

$$E\left[\frac{X_t}{N}\left(1-\frac{X_t}{N}\right)\right]=E\left(\frac{X_t}{N}\right)-E\left[\left(\frac{X_t}{N}\right)^2\right]=E\left(\frac{X_t}{N}\right)-V\left(\frac{X_t}{N}\right)-\left[E\left(\frac{X_t}{N}\right)\right]^2. \qquad \textbf{[S46]}$$

By the induction assumption, $V(X_t/N)\simeq(1/N)tx(1-x)$, and ignoring terms of order $1/N^2$, we have

$$E\left(\frac{X_{t+1}}{N}-\frac{X_t}{N}\right)\simeq\frac{1}{N}\rho s_{t+1}E\left(\frac{X_t}{N}\right)\left[1-E\left(\frac{X_t}{N}\right)\right]. \qquad \textbf{[S47]}$$

Applying **[S43]**, we have

$$\begin{aligned}E\left(\frac{X_t}{N}\right)&\simeq x+\frac{1}{N}\rho S_t x(1-x),\\ 1-E\left(\frac{X_t}{N}\right)&\simeq 1-x-\frac{1}{N}\rho S_t x(1-x),\end{aligned} \qquad \textbf{[S48]}$$

and ignoring terms $O(1/N^2)$, we find

$$E\left(\frac{X_{t+1}}{N}-\frac{X_t}{N}\right)\simeq\frac{1}{N}\rho s_{t+1}x(1-x). \quad \textbf{[S49]}$$

Thus,

$$\begin{aligned}E\left(\frac{X_{t+1}}{N}-x\right)&=E\left(\frac{X_{t+1}}{N}-\frac{X_t}{N}\right)+E\left(\frac{X_t}{N}-x\right)\\&\simeq\frac{1}{N}\rho s_{t+1}x(1-x)+\frac{1}{N}\rho S_t x(1-x),\end{aligned} \quad \textbf{[S50]}$$

and since $S_t+s_{t+1}=S_{t+1}$,

$$E\left(\frac{X_{t+1}}{N}-x\right)\simeq\frac{1}{N}\rho S_{t+1}x(1-x) \quad \textbf{[S51]}$$

as desired.

We now compute $V(X_{t+1}/N)$ using the induction assumption and the formula

$$V\left(\frac{X_{t+1}}{N}\right)=E\left[V\left(\frac{X_{t+1}}{N}\middle|X_t\right)\right]+V\left[E\left(\frac{X_{t+1}}{N}\middle|X_t\right)\right], \quad \textbf{[S52]}$$

where by [**S43**],

$$E\left(\frac{X_{t+1}}{N}\middle|X_t\right)\simeq\frac{X_t}{N}+\frac{1}{N}\rho s_{t+1}\frac{X_t}{N}\left(1-\frac{X_t}{N}\right) \quad \textbf{[S53]}$$

and

$$V\left(\frac{X_{t+1}}{N}\middle|X_t\right)\simeq\frac{1}{N}\frac{X_t}{N}\left(1-\frac{X_t}{N}\right). \quad \textbf{[S54]}$$

Here, we used the fact that $y'(1-y')\simeq y(1-y)$. Now,

$$E\left[V\left(\frac{X_{t+1}}{N}\middle|X_t\right)\right]\simeq\frac{1}{N}E\left[\frac{X_t}{N}\left(1-\frac{X_t}{N}\right)\right]\simeq\frac{1}{N}x(1-x), \quad \textbf{[S55]}$$

where we use the same computations as led from [**S46**] to [**S49**]:

$$V\left[E\left(\frac{X_{t+1}}{N}\middle|X_t\right)\right]=V\left[\frac{X_t}{N}+\frac{1}{N}\rho s_{t+1}\frac{X_t}{N}\left(1-\frac{X_t}{N}\right)\right]. \quad \textbf{[S56]}$$

Since $(X_t/N)\left[1-(X_t/N)\right]$ is a random variable taking values in [0,1], its variance is less than 1/4 and

$$V\left[\frac{1}{N}\rho s_{t+1}\frac{X_t}{N}\left(1-\frac{X_t}{N}\right)\right]\le\frac{1}{4N^2}\rho^2 s_{t+1}^2. \quad \textbf{[S57]}$$

We ignore terms $O(1/N^2)$, so that the random variable $(1/N)\rho s_{t+1}(X_t/N)\left[1-(X_t/N)\right]$ is almost constant. As a result,

$$V\left[E\left(\frac{X_{t+1}}{N}\middle|X_t\right)\right]\simeq V\left(\frac{X_t}{N}\right)\simeq\frac{1}{N}tx(1-x) \quad \textbf{[S58]}$$

by the induction assumption. Combining [**S55**] and [**S58**] gives

$$V\left(\frac{X_{t+1}}{N}\right)\simeq\frac{1}{N}x(1-x)+\frac{1}{N}tx(1-x)=\frac{1}{N}(t+1)x(1-x) \quad \textbf{[S59]}$$

as expected.

Calculation of Stable Vertical Transmission Rate in *AkBk*. Here, we describe the analysis of the stability of a modifier allele m with vertical transmission rate ρ to invasion by a modifier M with a vertical transmission rate P, as described in Eq. **32**, in environmental regime $AkBl$. The analysis is similar to that used in *Result 8* to analyze stability in $A1B1$, but it is numerical, because the cases where $k>1$ or $l>1$ require solving polynomials of degree >6 to obtain closed form expressions.

The analysis includes the following steps for fixed W, w, k, and l. First, we find the stable frequency of phenotype A with a single modifier x^*. This is done by minimizing the expression $|x_{k+l}-x_0|$, where x_t is defined in Eq. **9**. The minimization is done by iterating the recurrence in Eq. **9** until it converges (i.e., until the difference $|x_{k+l}-x_0|$ is smaller than available machine precision; roughly 10^{-8} when subtracting similar small numbers). Second, we set the frequency vector with two modifiers to $\underline{x}^*=(x^*,1-x^*,0,0)$ (that is, to the stable frequencies in the absence of modifier M).

Now, we define $F_A(\underline{x})$ by Eq. **32** with $w_A=W$ and $w_B=w$ ($W>w$), and similarly, we define $F_B(\underline{x})$ with $w_B=W$ and $w_A=w$. Also, we define, similar to Eq. **34**, $F(\underline{x})$ by composition

$$F=\underbrace{F_B\circ\cdots\circ F_B}_{l\text{ times}}\circ\underbrace{F_A\circ\cdots\circ F_A}_{k\text{ times}}. \quad \textbf{[S60]}$$

To obtain a linear approximation of $F(\underline{x})$ near $\underline{x}^*$, we calculate the Jacobian matrix of $F(\underline{x})$ at $\underline{x} = \underline{x}^*$,

$$\mathbf{J}_{ij} = \mathbf{J}(\underline{x}^*)_{ij} = \frac{\partial F(\underline{x}^*)_i}{\partial x_j}, \quad \textbf{[S61]}$$

and the 2×2 external stability matrix $\mathbf{L} = \mathbf{L}_{ex}$ is as in Eqs. **S29** and **S30** (note that the upper right block is $\underline{0}$, because $x_3^* = x_4^* = 0$):

$$\mathbf{J} = \begin{bmatrix} \mathbf{L}_{in} & \underline{0} \\ * & \mathbf{L}_{ex} \end{bmatrix}. \quad \textbf{[S62]}$$

We calculate the eigenvalues $\lambda_1 > \lambda_2$ of $\mathbf{L}$ using the quadratic formula, as the characteristic polynomial of $\mathbf{L}$ has degree 2. By the Perron–Frobenius theorem, the leading eigenvalue λ_1 is real and positive. Denote by $\lambda_1(\rho, P)$ the resulting leading eigenvalue with resident rate ρ and invader rate P. Note that, for any $\rho \in (0, 1)$,

$$\lambda_1(\rho, \rho) = 1. \quad \textbf{[S63]}$$

The evolutionarily stable rate ρ^* is defined to be stable to invasion; that is, for a small enough value $\partial P > 0$, we have

$$\lambda_1(\rho^*, \rho^* \pm \partial P) < 1 = \lambda_1(\rho^*, \rho^*), \quad \textbf{[S64]}$$

where the equality is given by Eq. **S63**. Therefore,

$$\frac{\partial \lambda_1}{\partial P}(\rho^*, \rho^*) = 0. \quad \textbf{[S65]}$$

We use Brent's (2) root-finding method to find ρ^* that satisfies Eq. **S65**. If, due to numerical instability of the described numerical process, we have

$$\partial \frac{\lambda_1}{\partial P}(0,0) \cdot \frac{\partial \lambda_1}{\partial P}(1,1) > 0 \quad \textbf{[S66]}$$

(i.e., the partial derivative sign is identical at $\rho = P = 0$ and $\rho = P = 1$), then we cannot use Brent's (2) method. In these cases, we assume that the partial derivative does not have a root in $(0, 1)$, and we determine the stable rate ρ^* by the rule

$$\rho^* = \begin{cases} 0 & \text{if } \frac{\partial \lambda_1}{\partial P}(0,0) \le 0 \\ 1 & \text{if } \frac{\partial \lambda_1}{\partial P}(0,0) > 0. \end{cases} \quad \textbf{[S67]}$$

Fig. S10 shows the sensitivity of the leading eigenvalue λ_1 of the external stability matrix $\mathbf{L}$ to changes in the invader rate P as a function of the resident rate ρ for different choices of environmental cycles $AkBk$.

The numerical analysis above is fine for small k, but for large k and especially for $w = 0.1$, the calculation is unstable. This is probably because when the environment is constant for a long period, most of the time the frequencies x_i are very close to the boundaries (i.e., zero and one).

Crucially, the Jacobian $\mathbf{J}$ in Eq. **S61** is calculated using automatic differentiation from a function that iteratively calculates $F(\underline{x}^*)$ according to Eq. **S60**. Similarly, the partial derivative $\frac{\partial \lambda_1}{\partial P}$ in Eq. **S65** is calculated from a function that calculates λ_1 using simple arithmetic operations. Note that automatic differentiation does not mean symbolic or numerical differentiation, which can lead to inefficient or inaccurate estimation of $\mathbf{J}$ when k is not very small. Rather, from ref. 3, "Automatic differentiation is a set of techniques for transforming a program that calculates numerical values of a function, into a program which calculates numerical values for derivatives of that function with about the same accuracy and efficiency as the function values themselves."

Diffusion Approximation. We compute the mean $\mu(x)$ and the variance $\sigma^2(x)$ of the change in one generation in the frequency of phenotype A given that, at the beginning of the generation, $X_t = Nx$. To compute $\mu(x)$, observe that, by Eq. **40**,

$$x' - x = \frac{w_A x}{\overline{w}}\rho + (1-\rho)x - x = \rho x\left[\frac{w_A}{\overline{w}} - 1\right] = \rho x(1-x)\frac{w_A - w_B}{w_A x + w_B(1-x)}, \quad \textbf{[S68]}$$

since $\overline{w} = w_A x + w_B(1-x)$. For the diffusion approximation, it is essential that the differential selection does not have a large effect per individual in each time period Δt $\left(\Delta t \simeq \frac{1}{N}\right)$. That is, we assume that

$$w_A - w_B = \frac{s}{N}. \quad \textbf{[S69]}$$

Then,

$$x' - x \simeq \frac{1}{N}\rho s x(1-x) \quad \textbf{[S70]}$$

up to terms of order small than $\frac{1}{N}$. Since one generation corresponds to $\Delta t \simeq \frac{1}{N}$, we conclude that

$$\mu(x) = \rho s x(1-x); \quad 0 \le x \le 1. \quad \textbf{[S71]}$$

In the same way, we can compute

$$\sigma^2(x) = x(1-x). \quad \textbf{[S72]}$$

1. Ewens W (2004) Mathematical Population Genetics (Springer, New York), 2nd Ed.
2. Brent RP (1971) An algorithm with guaranteed convergence for finding a zero of a function. *Comput J* 14:422–425.
3. Bartholomew-Biggs M, Brown S, Christianson B, Dixon L (2000) Automatic differentiation of algorithms. *J Comput Appl Math* 124:171–190.

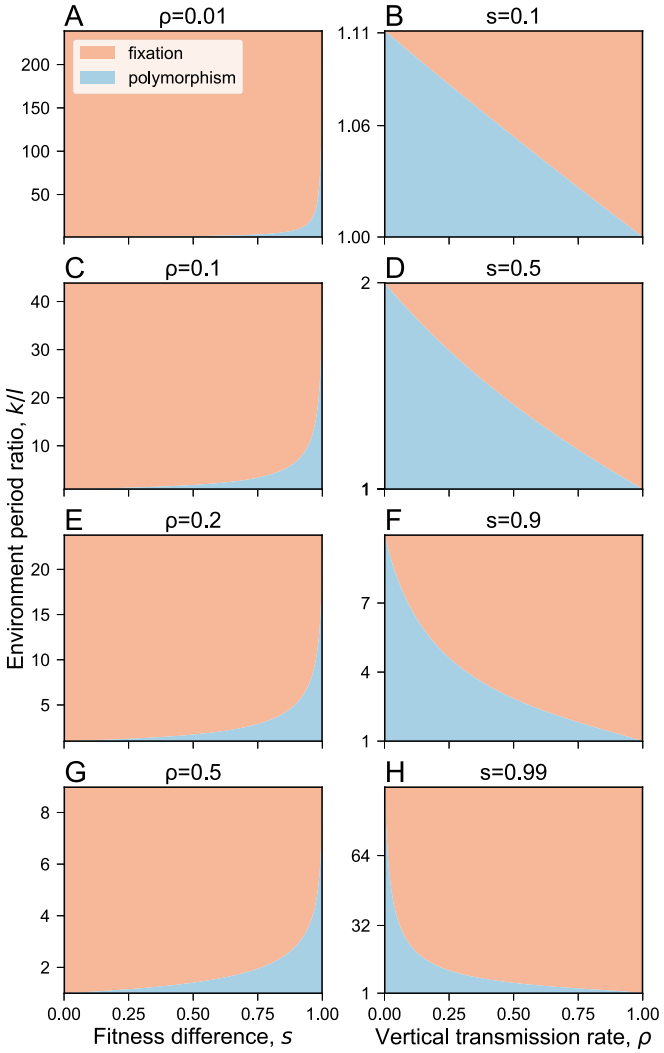

Fig. S1. Ratios of selection periods $\frac{k}{l}$ that lead to fixation of phenotype *A* (red) or polymorphism of phenotypes *A* and *B* (blue); *k* and *l* are the numbers of generations in which phenotypes *A* and *B*, respectively, are favored by selection. In all cases, $W = 1$, and $w = 1 - s$. *A*, *C*, *E*, and *G* are for different ρ values and *B*, *D*, *F*, and *H* are for different *s* values.

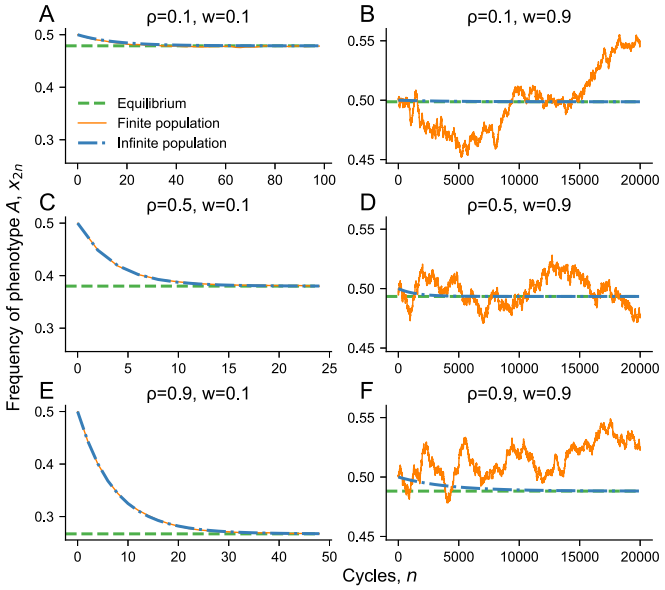

Fig. S2. Frequency of phenotype *A* after every two generations in selection regime *A*1*B*1. The orange line is the finite population model (Eqs. **40** and **41**) (average of 100 simulations). The blue line is the infinite population model (Eq. **21**), and the green line is the solution of $Q(x) = 0$ (Eq. **22**). In all cases, $W = 1$; for the finite population model (orange lines), population size is $N = 10,000$, and initial frequency of *A* is $x_0 = 0.5$. *A*–*F* are for the shown values of ρ and w.

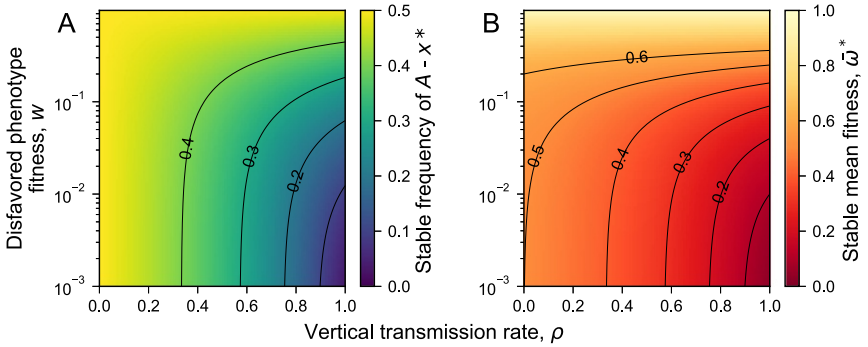

Fig. S3. Properties of stability in *A1B1* selection regime. (*A*) Stable frequency of phenotype *A* and (*B*) stable mean fitness as functions of the vertical transmission rate ρ and the fitness of the disfavored phenotype w. Black contour lines join ρ and w combinations that result in the same stable value. In all cases, fitness of the favored phenotype is $W = 1$.

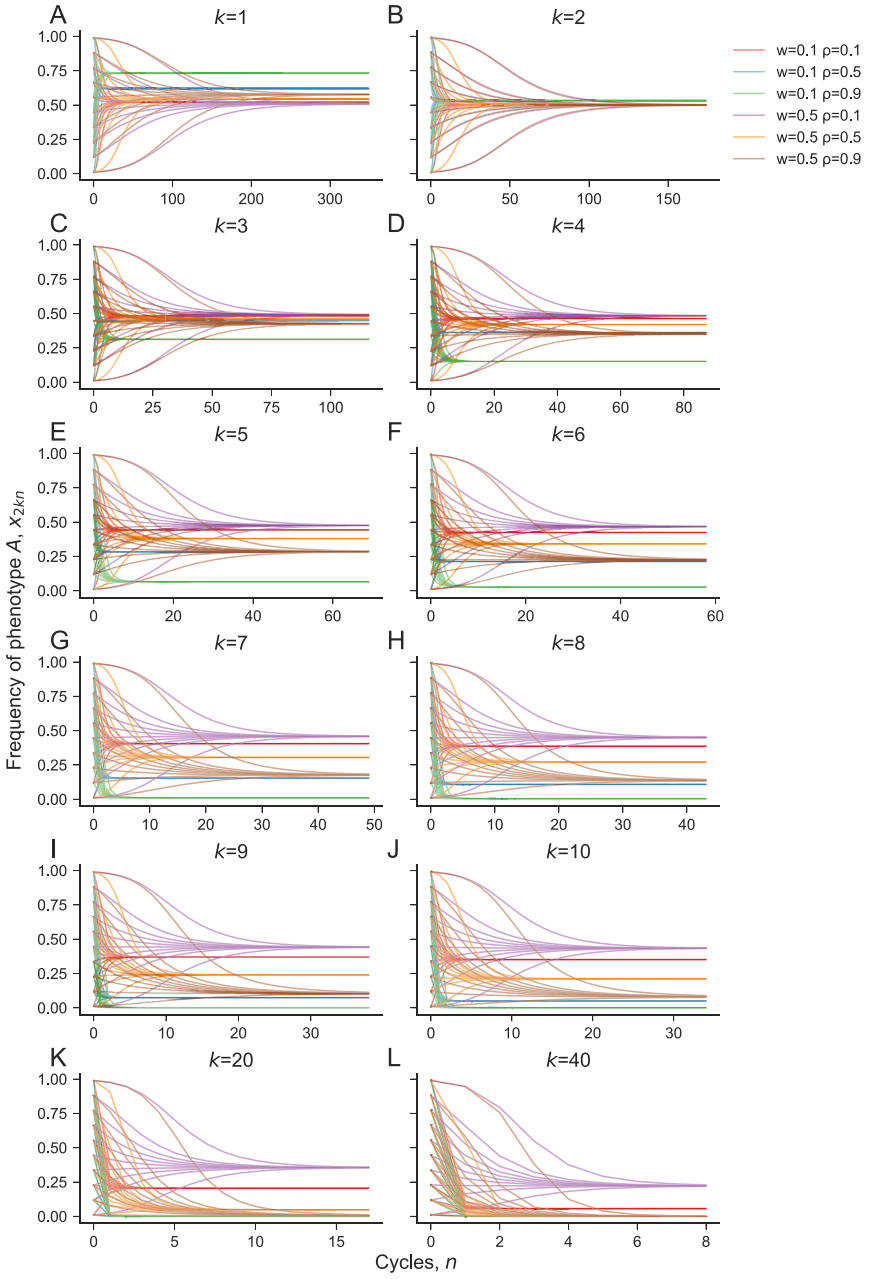

Fig. S4. Convergence of the frequency of phenotype *A* to a stable polymorphism in selection regime *AkBk*. Comparison of dynamics starting with different initial frequencies of phenotype *A* (0.01–0.99) and different *k*, ρ, and *w* values. The lines show the *x* frequency of phenotype *A* at the end of each period after every 2*k* generations. In all cases, $W = 1$. *A*–*L* are for the specified value of *k*.

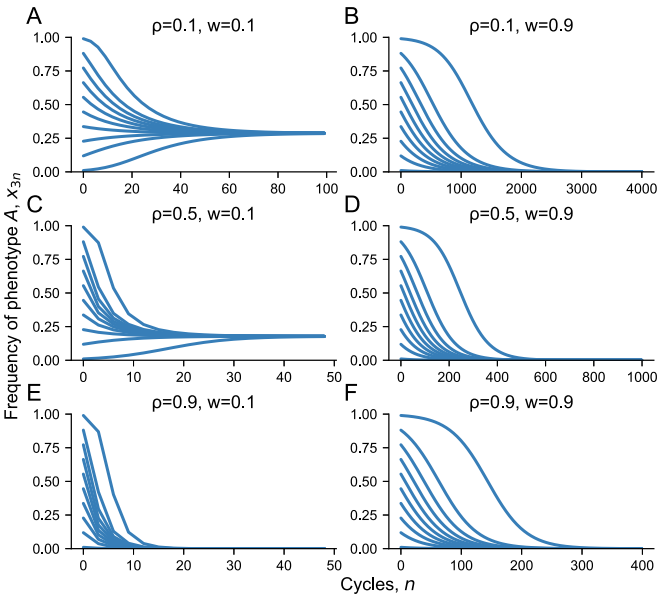

Fig. S5. Frequency of phenotype *A* after every three generations in selection regime *A*1*B*2. Comparison of dynamics starting with different initial frequency of phenotype *A* (0.01–0.99) (Figs. 1 and 7). In all cases, $W = 1$. *A*–*F* are for the specified values of ρ and w.

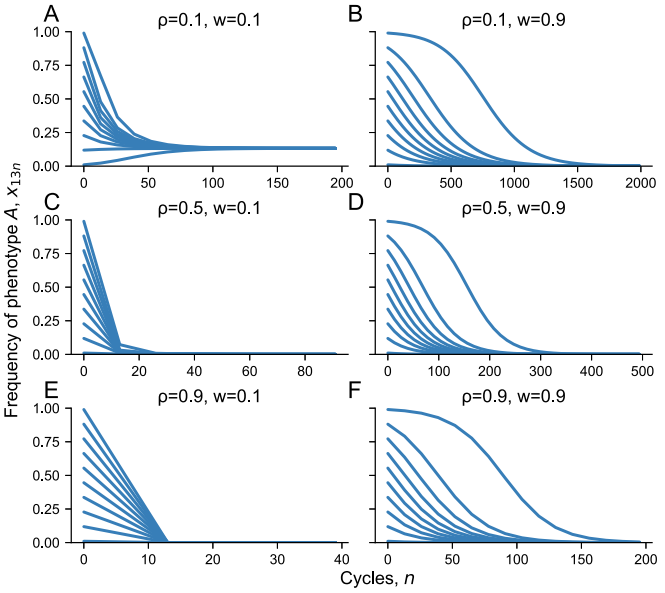

Fig. S6. Frequency of phenotype *A* after every 13 generations in selection regime *A*3*B*10. Comparison of dynamics starting with different initial frequency of phenotype *A* (0.01–0.99). In all cases, $W = 1$. *A*–*F* are for the specified values of ρ and w.

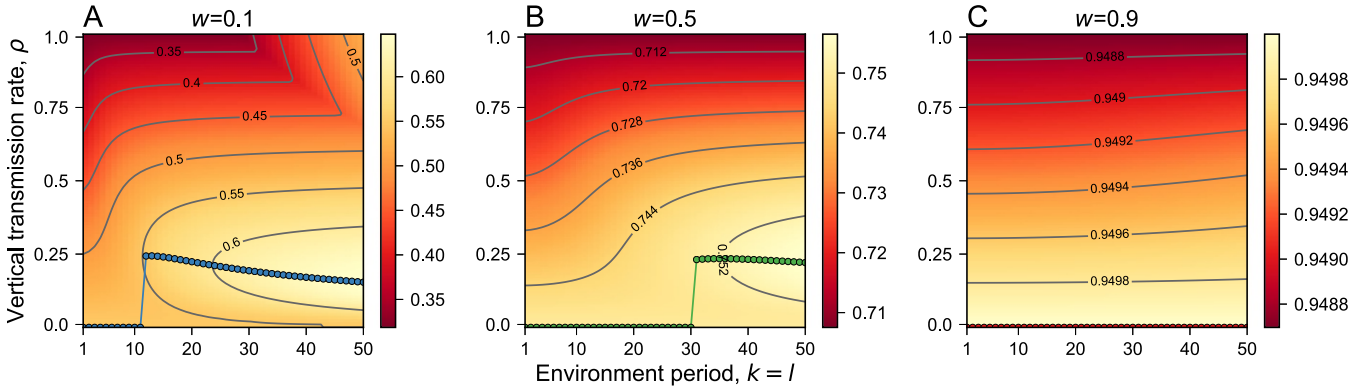

Fig. S7. Stable population mean fitness in selection regime *AkBk* as a function of the vertical transmission rate ρ and the number k of generations in which phenotypes A and B are favored by selection for different selection intensities: (A) $w = 0.1$, (B) $w = 0.5$, and (C) $w = 0.9$. Colors represent the geometric average of the stable population mean fitness over $2k$ generations calculated by iterating Eq. **9** until phenotype frequencies stabilized and for at least 1, 000 generations. Blue markers show the maximum average mean fitness for each period k. For example, with $w = 0.1$, $\hat{\rho} = 0$ maximizes the average fitness for $k \leq 11$; then, $\hat{\rho}$ increases to $\hat{\rho} \approx 0.24$ and continues to decrease as k increases, down to $\hat{\rho} \approx 0.15$ for $k = 50$ (Fig. 6). Contour lines represent ρ and k combinations that produce the same average mean fitness. In all cases, $W = 1$.

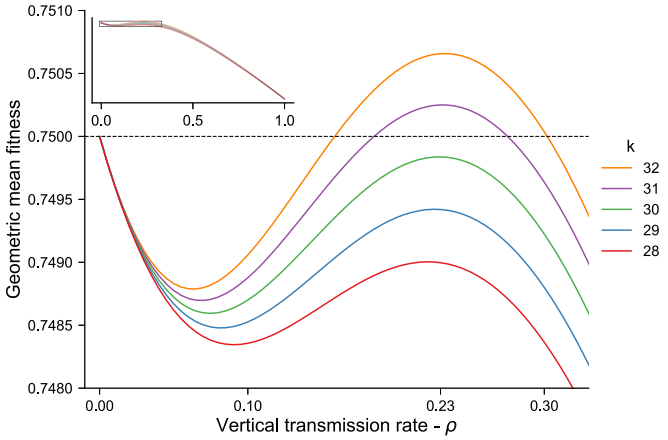

Fig. S8. The geometric average of the stable population mean fitness over the $2k$ generation period peaks at $\rho = 0$ for $k \leq 30$ (red, blue, and green lines) and at $\rho \approx 0.23$ for $k = 31$ and 32 (purple and orange lines, respectively) (Fig. 6). *Inset* zooms out to show that the geometric mean fitness is strictly and significantly decreasing for $\rho > 0.3$ (reaching ≈ 0.7 for $\rho = 1$). In all cases, $W = 1$ and $w = 0.5$.

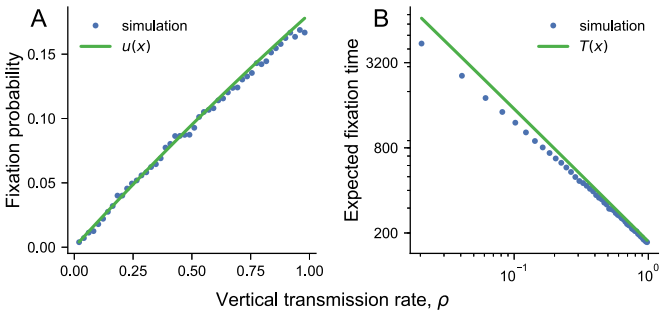

Fig. S9. Fixation probability and mean time in a finite population. (A) Fixation probability $u(x)$ of phenotype A (Eq. **42**). (B) Expected time to fixation $T(x)$ of phenotype A (Eq. **43**) conditioned on its fixation, starting with a single copy in a population of size N. The figure compares two estimates: Wright–Fisher simulations (blue circles) and diffusion equation approximation (green solid lines). Parameters: selection coefficient, $s = w_A - w_B = 0.1$; population size, $N = 10, 000$.

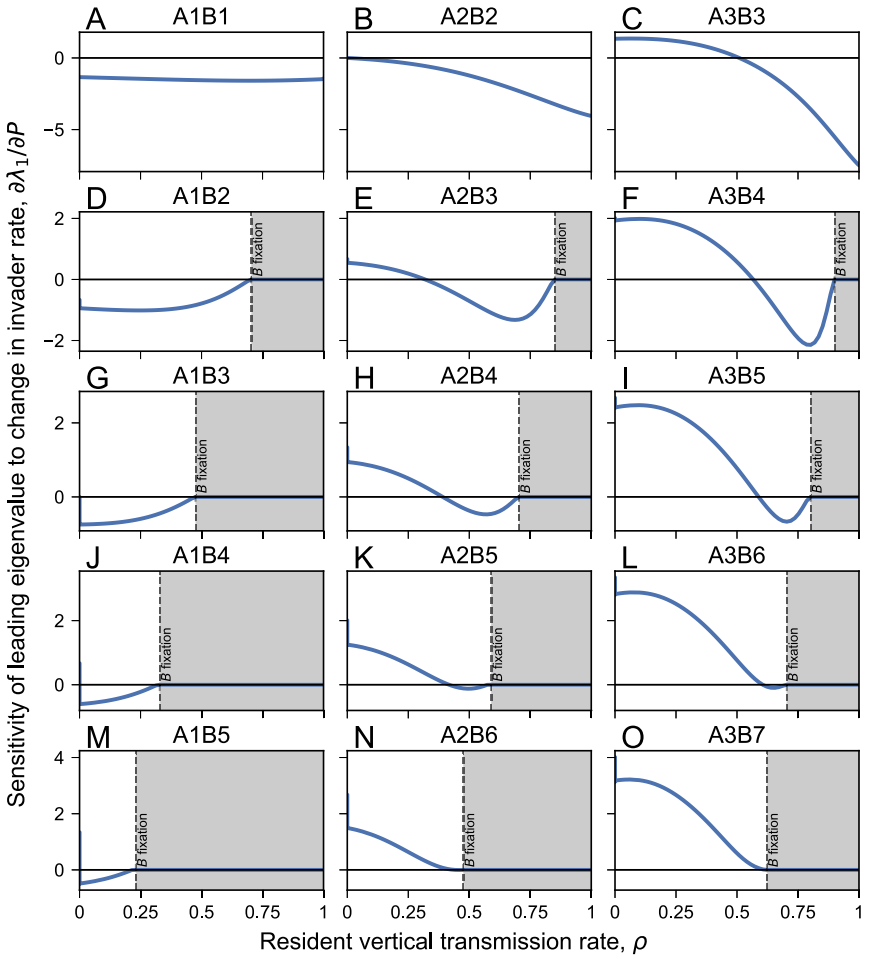

Fig. S10. Evolutionarily stable vertical transmission rate in *AkBl* selection regime. The figure shows $\frac{\partial\lambda_1}{\partial P}$, the sensitivity of the leading eigenvalue of the external stability matrix **L** to changes in *P* (the vertical transmission rate of the invader allele) as a function of ρ, the vertical transmission rate of the resident allele (details are in *Evolutionary Stability of Oblique Transmission* and *SI Text*). The shaded areas mark ρ values for which phenotype *B* fixes and there is no polymorphism (Eq. **20**). Without polymorphism, selection does not affect the transmission rate, and therefore, any rate in the shaded areas is neutrally stable. In *A*, *B*, *D*, *G*, *J*, and *M*, $\frac{\partial\lambda_1}{\partial P} < 0$ at the vicinity of $\rho = 0$, and therefore, the stable rate is $\rho^* = 0$. In *B*, *C*, *E*, *F*, *H*, *I*, *K*, and *L*, the stable rate ρ^* can be identified as the ρ value at which $\frac{\partial\lambda_1}{\partial P}$ changes from positive to negative. In *N* and *O*, $\frac{\partial\lambda_1}{\partial P} > 0$ for all ρ values that protect polymorphism, and therefore, there are only neutrally stable rates (in the shaded areas). Here, $W = 1$ and $w = 0.1$.

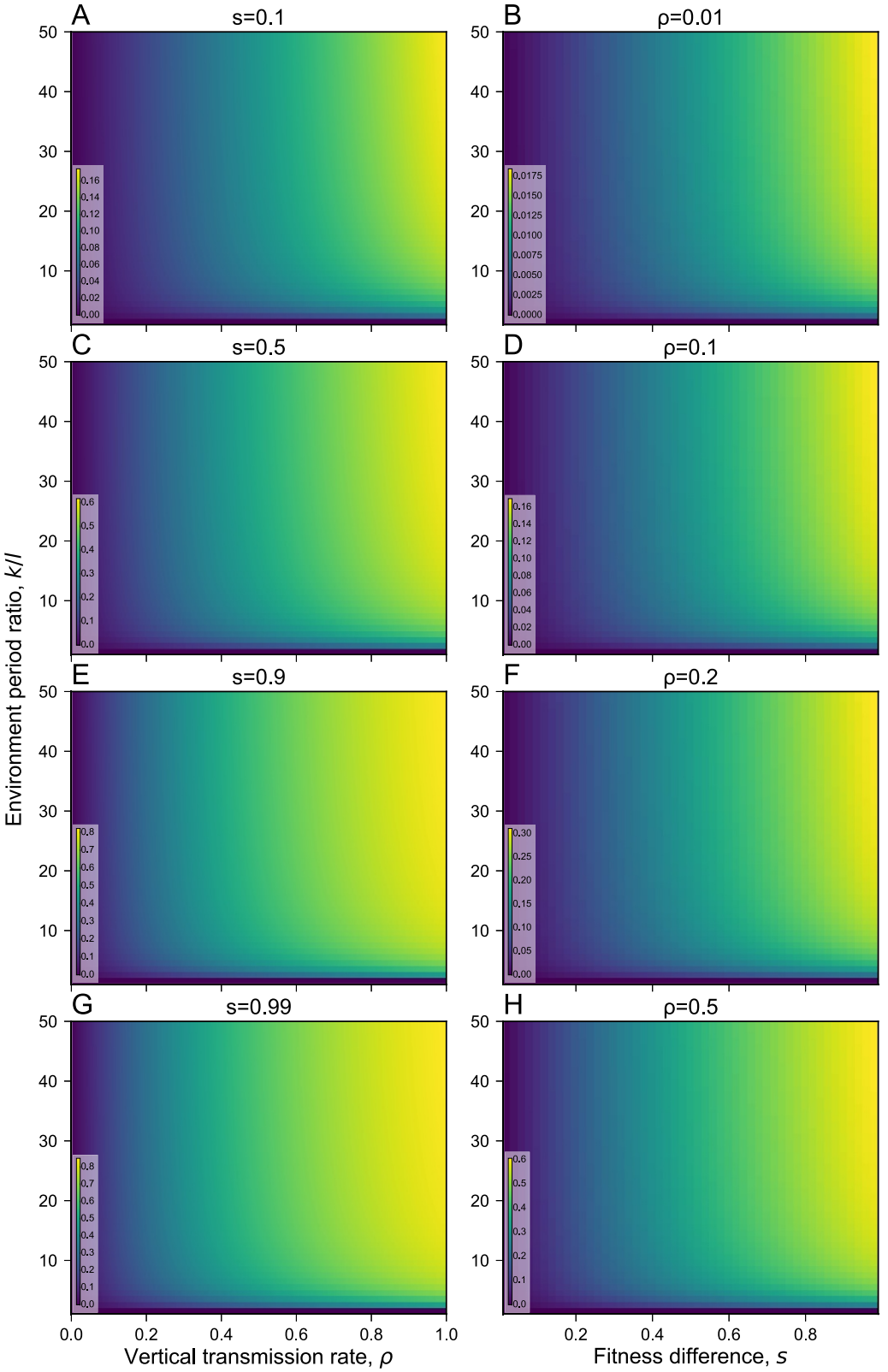

Fig. S11. Fixation in a finite population with different ratios of selection periods $\frac{k}{l}$. Fixation probability of phenotype *A* when starting with a single copy in a population of size *N*: $u(1/N) = (1 - \exp(-2\rho\,\frac{k-l}{k+l}(W - w))/(1 - \exp(-2N\rho\,\frac{k-l}{k+l}(W - w))$ (Eqs. **46** and **47**); *k* and *l* are the numbers of generations in which phenotypes *A* and *B*, respectively, are favored by selection. In all cases, fitness of the favored phenotype is $W = 1$; fitness of the unfavored phenotype is $w = 1 - s$, and the population size is $N = 10{,}000$. *A*, *C*, *E*, and *G* are for the specified value of *s* and *B*, *D*, *F*, and *H* are for the specified value of ρ.

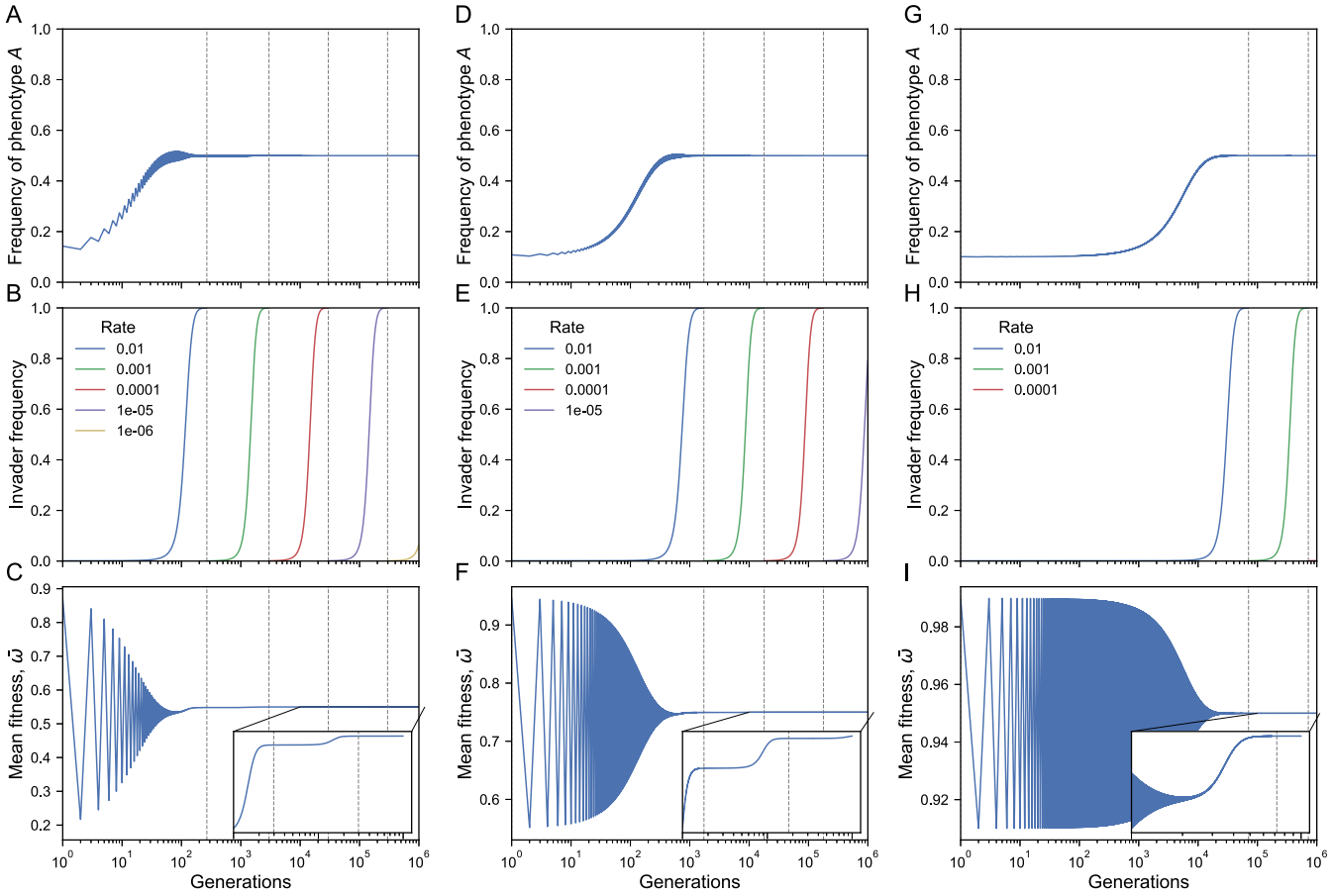

Fig. S12. Consecutive fixation of modifiers that reduce the vertical transmission rate in selection regime *A1B1*. The figure shows results of numerical simulations of evolution with two modifier alleles (Eq. **32**). When a modifier allele fixes (frequency >99.9%), a new modifier allele is introduced with a vertical transmission rate one order of magnitude lower (vertical dashed lines). (*A*, *D*, and *G*) The frequency of phenotype *A* in the population over time. (*B*, *E*, and *H*) The frequency of the invading modifier allele over time. (*C*, *F*, and *I*) The population geometric mean fitness over time; *Insets* zoom in to show that the mean fitness decreases slightly with each invasion. Invading alleles are introduced at frequency 0.01%; whenever their frequency drops below 0.01%, they are reintroduced. Parameters: vertical transmission rate of the initial resident modifier allele, $\rho_0 = 0.1$; fitness values: $W = 1$ and $w = 0.1$ (*A*–*C*), 0.5 (*D*–*F*), and 0.9 (*G*–*I*). The *x* axis is on a log scale, as each sequential invasion takes an order of magnitude longer to complete. *D*–*F* are the same as in Fig. 4.