Supporting Information

Ram et al. 10.1073/pnas.1719171115

SI Text

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

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

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

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

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

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,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Then,

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

Summation yields

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

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

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

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,

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

and

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

Thus, **[S15]** implies that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$\frac{1}{t}\log\frac{x_t(\xi)}{x_0} \leq \frac{\mu}{4}, \tag{S27}$$

or for all $t \geq T$,

$$x_t(\xi) \leq x_0 \exp\left(\frac{\mu}{4}t\right). \tag{S28}$$

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

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

and

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

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

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

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,

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

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

$$\begin{bmatrix} x_1^* \\ x_2^* \end{bmatrix} = \mathbf{L}_2 \cdot \mathbf{L}_1 \begin{bmatrix} x_1^* \\ x_2^* \end{bmatrix} = \mathbf{L}\begin{bmatrix} x_1^* \\ x_2^* \end{bmatrix}. \tag{S33}$$

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

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

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

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

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]**,

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

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

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

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 $\underline{x} = \underline{x}^*$,

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

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 $x_3^* = x_4^* = 0$):

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

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 $\rho \in (0,1)$,

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

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

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

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

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

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

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

(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

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

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**,

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

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

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

Then,

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

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

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

In the same way, we can compute

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

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.

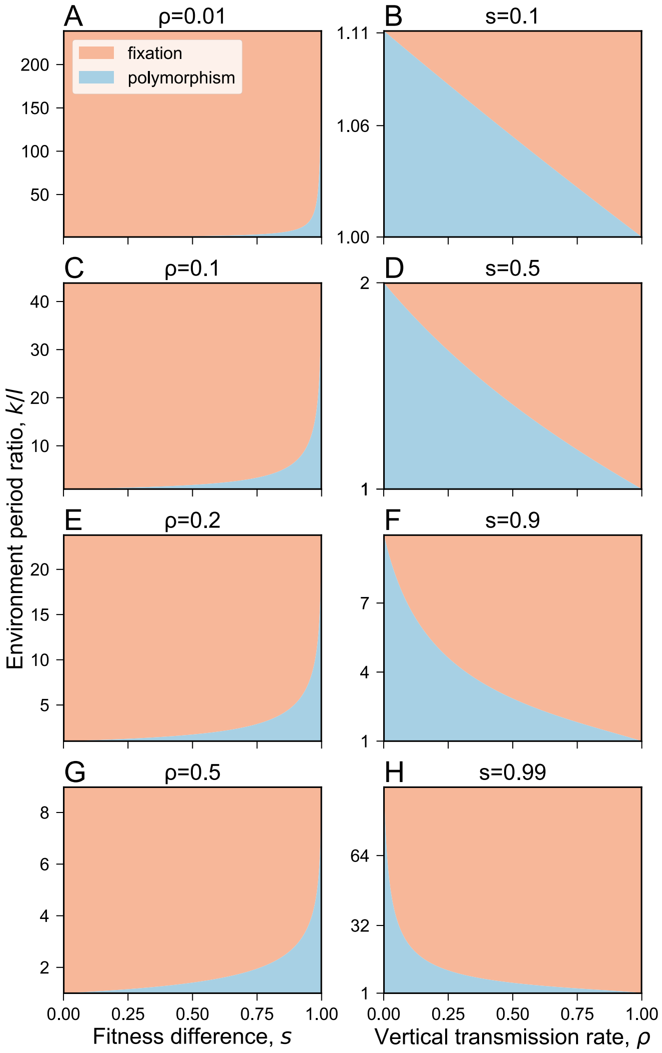

Fig. S1. Ratios of selection periods $\frac{k}{l}$ that lead to fixation of phenotype *A* (red) or polymorphism of phenotypes *A* and *B* (blue); *k* and *l* are the numbers of generations in which phenotypes *A* and *B*, respectively, are favored by selection. In all cases, $W = 1$, and $w = 1 - s$.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

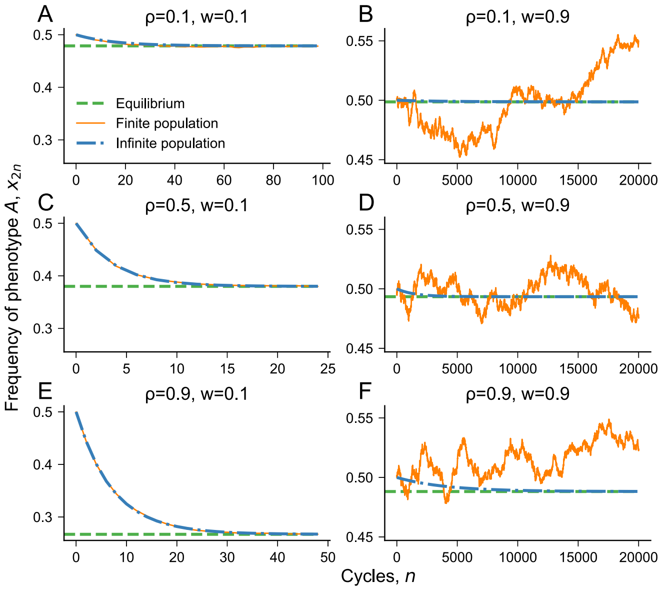

Fig. S2. Frequency of phenotype *A* after every two generations in selection regime *A*1*B*1. The orange line is the finite population model (Eqs. **40** and **41**) (average of 100 simulations). The blue line is the infinite population model (Eq. **21**), and the green line is the solution of $Q(x) = 0$ (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*.

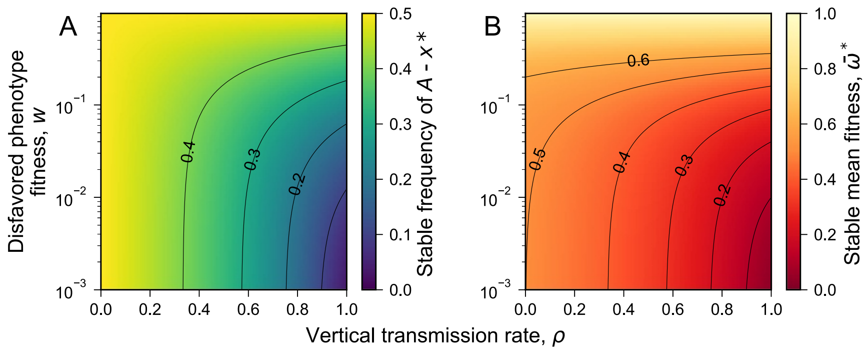

Fig. S3. Properties of stability in *A1B1* selection regime. (*A*) Stable frequency of phenotype *A* and (*B*) stable mean fitness as functions of the vertical transmission rate ρ and the fitness of the disfavored phenotype *w*. Black contour lines join ρ and *w* combinations that result in the same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

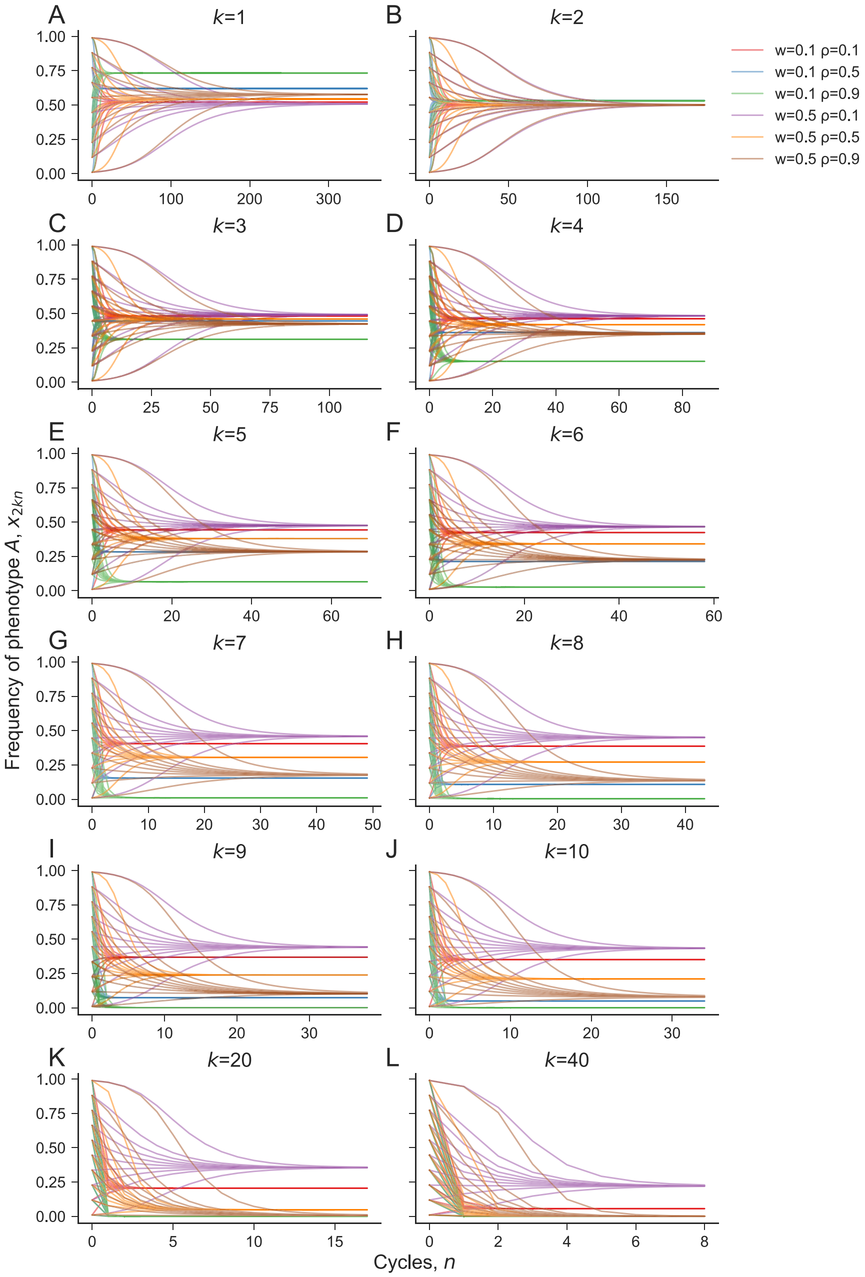

Fig. S4. Convergence of the frequency of phenotype A to a stable polymorphism in selection regime $AkBk$. Comparison of dynamics starting with different initial frequencies of phenotype A (0.01–0.99) and different k, ρ, and w values. The lines show the x frequency of phenotype A at the end of each period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

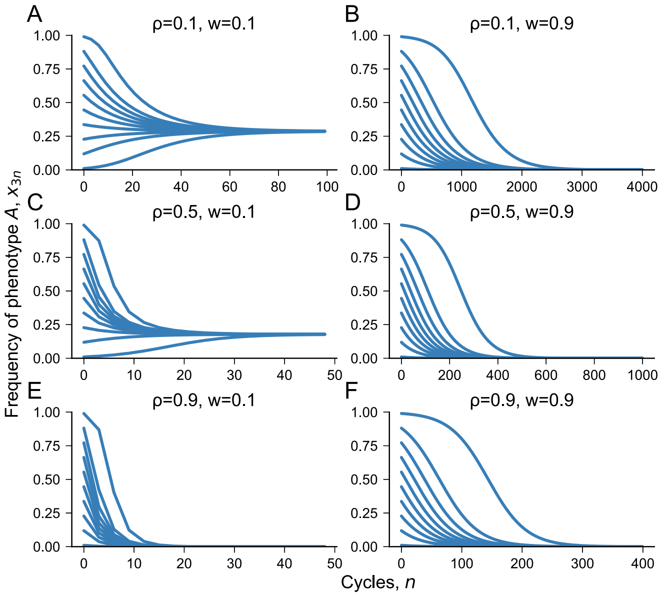

Fig. S5. Frequency of phenotype *A* after every three generations in selection regime *A*1*B*2. Comparison of dynamics starting with different initial frequency of phenotype *A* (0.01–0.99) (Figs. 1 and 7). In all cases, $W = 1$. *A*–*F* are for the specified values of ρ and *w*.

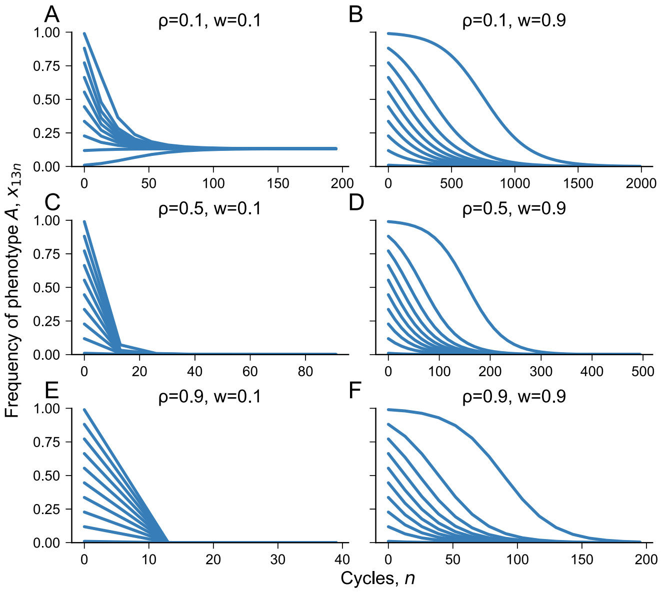

Fig. S6. Frequency of phenotype *A* after every 13 generations in selection regime *A*3*B*10. Comparison of dynamics starting with different initial frequency of phenotype *A* (0.01–0.99). In all cases, $W = 1$. *A*–*F* are for the specified values of ρ and *w*.

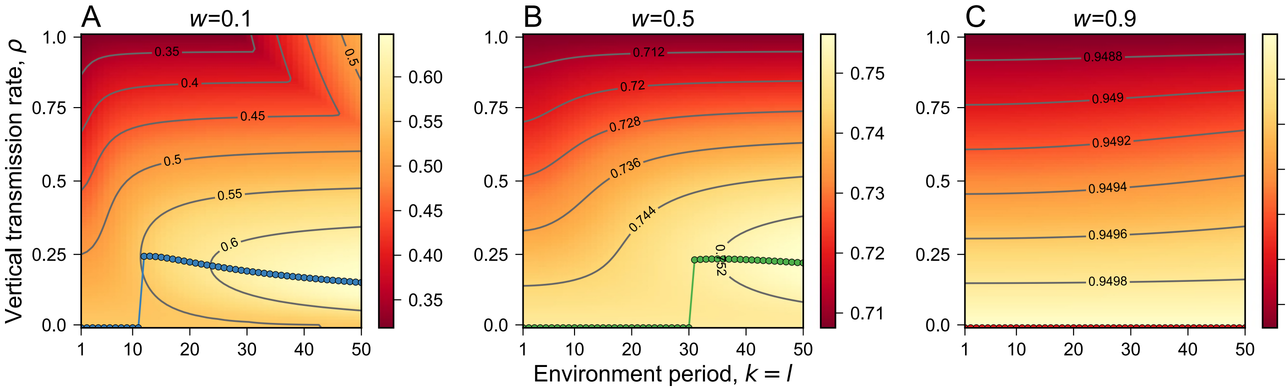

Fig. S7. Stable population mean fitness in selection regime *AkBk* as a function of the vertical transmission rate ρ and the number k of generations in which phenotypes *A* and *B* are favored by selection for different selection intensities: (*A*) $w = 0.1$, (*B*) $w = 0.5$, and (*C*) $w = 0.9$. Colors 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, $W = 1$.

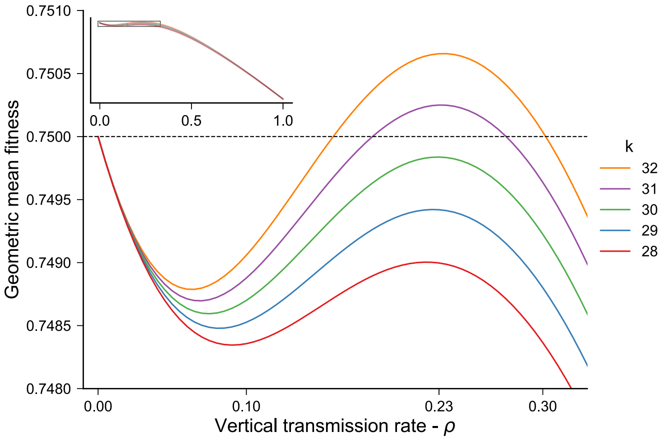

Fig. S8. The geometric average of the stable population mean fitness over the $2k$ generation period peaks at $\rho = 0$ for $k \leq 30$ (red, blue, and green lines) and at $\rho \approx 0.23$ for $k = 31$ and 32 (purple and orange lines, respectively) (Fig. 6). *Inset* zooms out to show that the geometric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

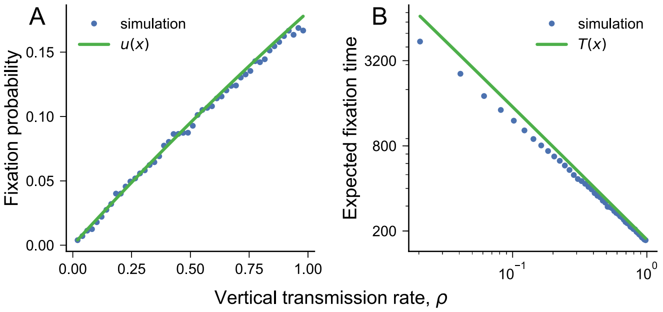

Fig. S9. Fixation probability and mean time in a finite population. (*A*) Fixation probability $u(x)$ of phenotype *A* (Eq. **42**). (*B*) Expected time to fixation $T(x)$ of phenotype *A* (Eq. **43**) conditioned on its fixation, starting with a single copy in a population of size *N*. The figure compares 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, $N = 10, 000$.

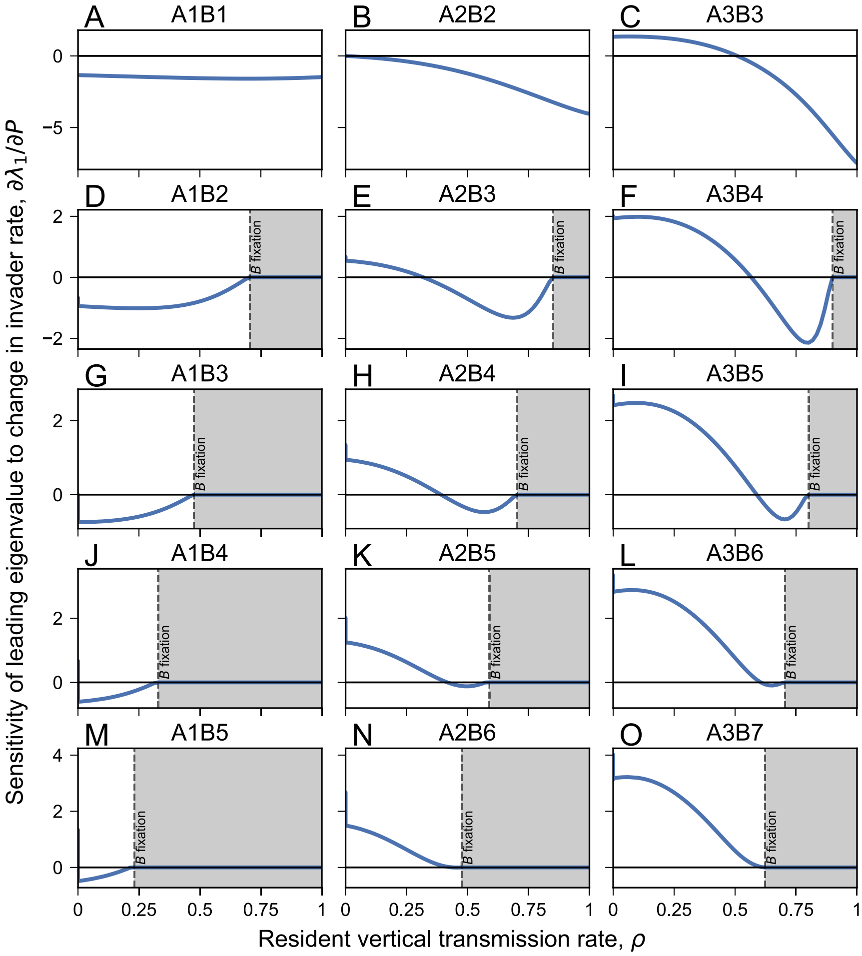

Fig. S10. Evolutionarily stable vertical transmission rate in *AkBl* selection regime. The figure shows $\frac{\partial \lambda_1}{\partial P}$, the sensitivity of the leading eigenvalue of the external stability matrix **L** to changes in *P* (the vertical transmission rate of the invader allele) as 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 $w = 0.1$.

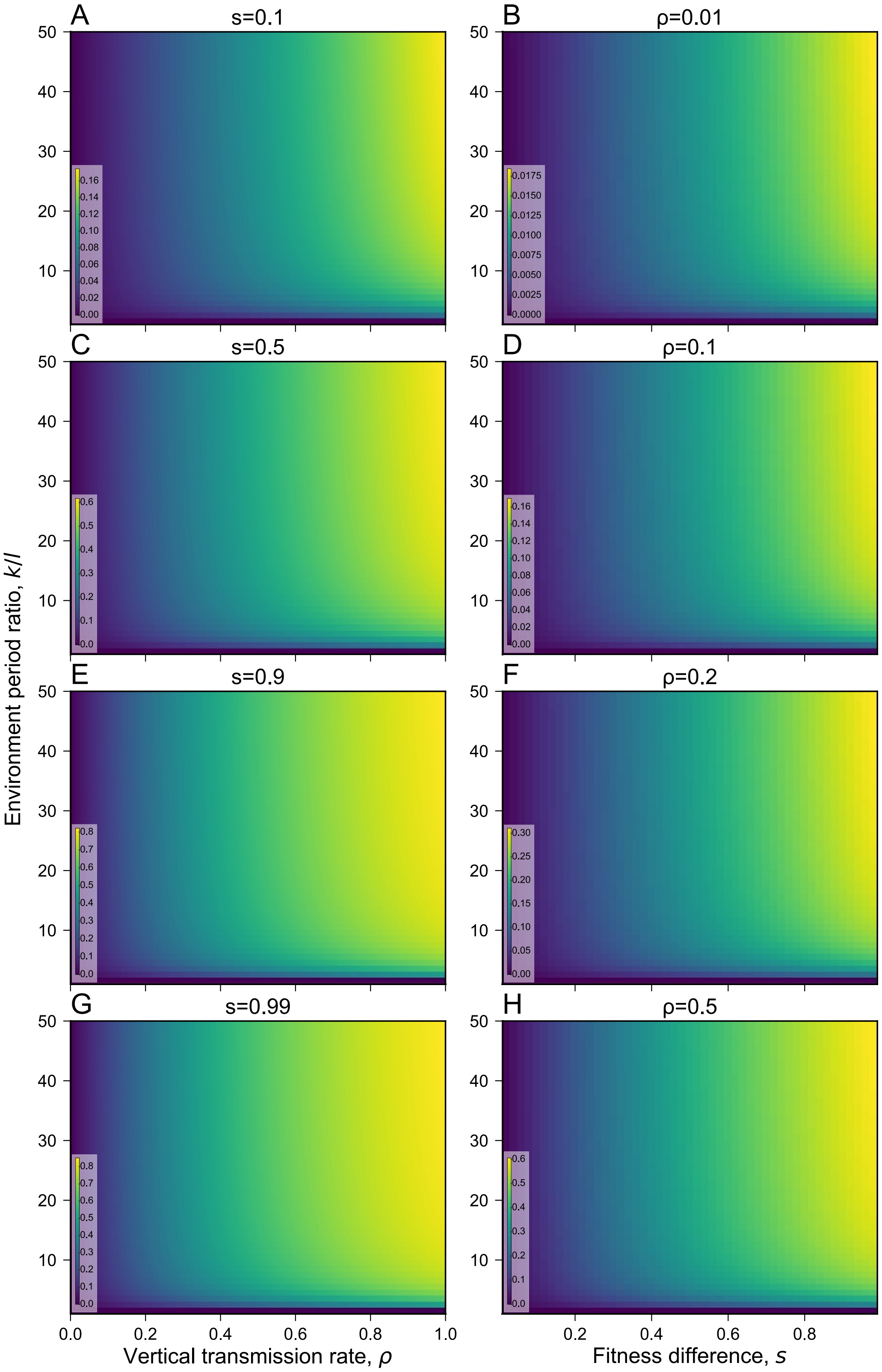

Fig. S11. Fixation in a finite population with different ratios of selection periods $\frac{k}{l}$. Fixation probability of phenotype *A* when starting with a single copy in a population of size *N*: $u(1/N) = (1 - \exp(-2\rho\,\frac{k-l}{k+l}(W - w))/(1 - \exp(-2N\rho\frac{k-l}{k+l}(W - w))$ (Eqs. **46** 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.

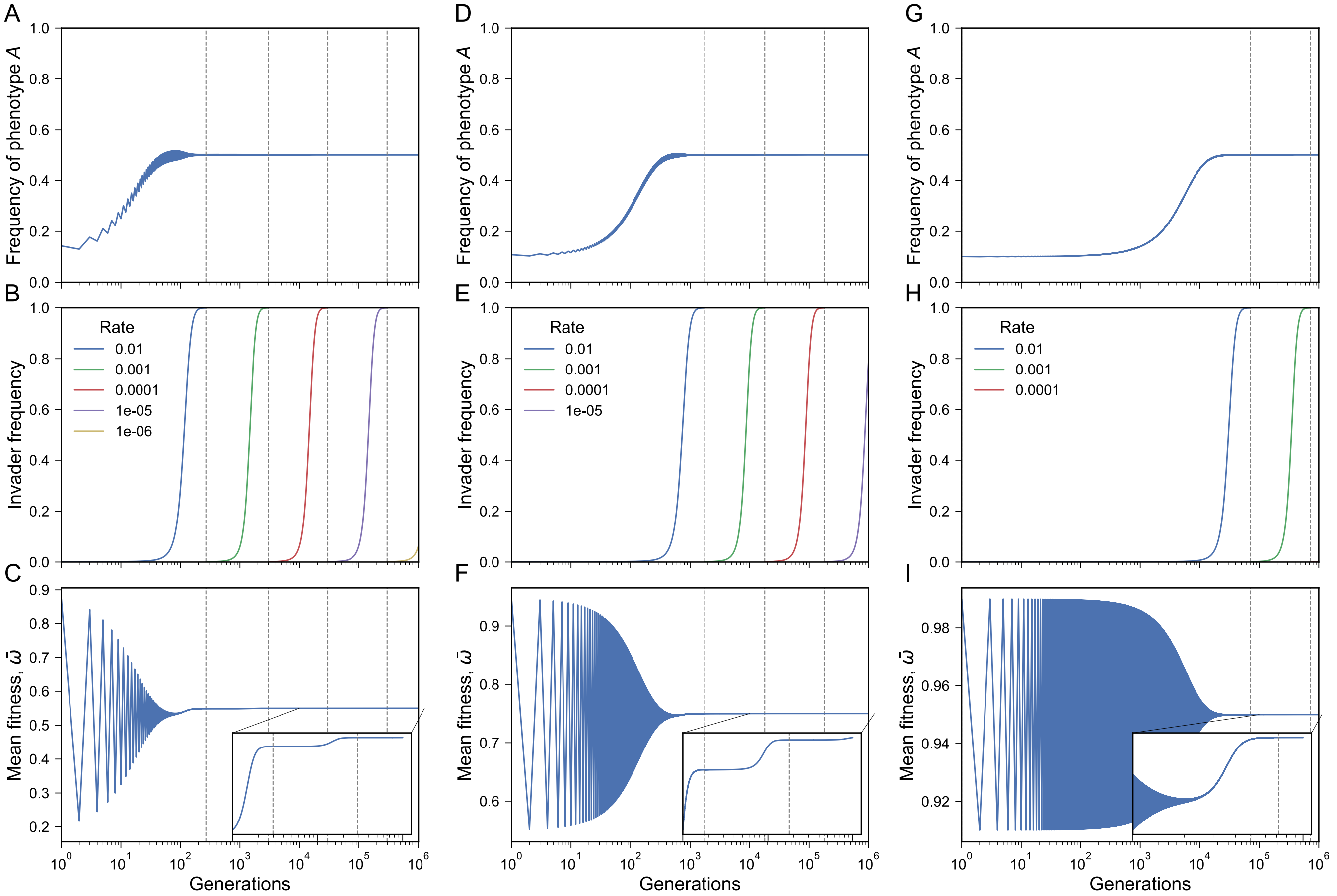

Fig. S12. Consecutive fixation of modifiers that reduce the vertical transmission rate in selection regime *A1B1*. The figure shows results of numerical simulations of evolution with two modifier alleles (Eq. **32**). When a modifier allele fixes (frequency >99.9%), a new modifier allele is introduced 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.