Natural selection and the advantage of recombination

Supplemental Information

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1 Groundwork: Evolutionary dynamics

We begin with some developments that will become necessary background material for other results. Variants of our one-locus model have appeared elsewhere by ourselves and others [6, 8, 5, 4, 1, 2], but we believe our characteristic-function (Fourier) framework, our two-locus model and our derivation of covariance dynamics is new.

1.1 Deterministic dynamics 1: One-locus model

1.1.1 Evolution of the distribution of fitnesses

Let $u(x,t)$ denote probability density in fitness x at time t (i.e., $\int_x u(x,t) = 1$ for all t) for an evolving population. Under selection and mutation, u evolves as:

$$\partial_t u(x,t) = (x - \bar{x})u(x,t) + U\int_\gamma u(x-\gamma,t)g(\gamma,t) - Uu(x,t)$$

where U is genomic mutation rate, and $g(\gamma,t)$ is probability density for fitness changes incurred by mutation, i.e., $g(\gamma,t)$ is the "distribution of fitness effects" of newly-arising mutations, or DFE.

1.1.2 Evolution of the corresponding characteristic function

Let $C(\varphi,t)$ denote the characteristic function for $u(x,t)$, i.e., $C(\varphi,t) = \int e^{i\varphi x}u(x,t)dx$ and let $M(\varphi,t)$ denote the characteristic function for the DFE, i.e., $M(\varphi,t) = \int e^{i\varphi x}g(x,t)dx$. The transformed equation is:

$$\partial_t C(\varphi,t) = -i\partial_\varphi C(\varphi,t) + i\partial_\varphi C(0,t)C(\varphi,t) + UC(\varphi,t)(M(\varphi,t) - 1).$$

Over the time interval in question (assumed to be short on evolutionary time scales), we will suppose the DFE is invariant such that $M(\varphi,t) = M(\varphi)$. Let $\Phi(\varphi,t) = \ln C(\varphi,t)$; then we have:

$$\partial_t \Phi(\varphi,t) = -i\partial_\varphi \Phi(\varphi,t) + i\partial_\varphi \Phi(0,t) + U(M(\varphi) - 1).$$

This equation is a variant of the transport equation and, when boundary condition $\Phi(0,t) = 0$ is applied, it has solution:

$$\Phi(\varphi,t) = \Phi(\varphi - it,0) - \Phi(-it,0) - iU\int_{\varphi-it}^{\varphi}(M(\gamma)-1)d\gamma + iU\int_{-it}^{0}(M(\gamma)-1)d\gamma$$

which reduces to:

$$\Phi(\varphi,t) = \Phi(\varphi - it,0) - \Phi(-it,0) - iU\int_{-it}^{0}(M(\varphi+\gamma) - M(\gamma))d\gamma \tag{1}$$

1.1.3 Dynamics of mean fitness

Mean fitness at time t, denoted $\bar{x}(t)$, is derived as follows:

$$\bar{x}(t) = (-i)\frac{\partial}{\partial\varphi}\left[\Phi(\varphi,t)\right]_{\varphi=0}$$

Letting $\Phi_0(\varphi) = \Phi(\varphi,0)$, this gives a general expression for mean fitness evolution under selection and mutation:

$$\bar{x}(t) = -i\Phi_0'(-it) + U[M(-it) - 1] \tag{2}$$

where the prime denotes derivative.

1.1.4 Dynamics of fitness variance and higher cumulants

Fitness variance at time t, denoted $\sigma_x^2(t)$, is derived as follows:

$$\sigma_x^2(t) = (-i)^2\frac{\partial^2}{\partial\varphi^2}\left[\Phi(\varphi,t)\right]_{\varphi=0}$$

giving:

$$\sigma_x^2(t) = -\Phi_0''(-it) - iU[M'(-it) - M'(0)] \tag{3}$$

And generally, the j^{th} cumulant at time t, denoted $\kappa_j(t)$, is given by:

$$\kappa_j(t) = (-i)^j\frac{\partial^j}{\partial\varphi^j}\left[\Phi(\varphi,t)\right]_{\varphi=0} \tag{4}$$

1.1.5 Connection to classical theory

Without mutation, the equation for mean fitness evolution is:

$$\bar{x}(t) = -i\Phi_0'(-it)$$

which may be rewritten as:

$$\begin{aligned}\bar{x}(t) &= -i\frac{\partial}{\partial\varphi}\left[i\kappa_1\varphi - \frac{1}{2}\kappa_2\varphi^2 - i\frac{1}{6}\kappa_3\varphi^3 + ...\right]_{\varphi=-it}\\ &= -i\left[i\kappa_1 + \kappa_2 it + \mathcal{O}(t^2) + ...\right]\end{aligned}$$

Noting that $\kappa_1 = \bar{x}(0)$ and $\kappa_2 = \sigma_x^2(0)$, and computing for some very small time increment into the future, $t = dt$, we have:

$$\begin{aligned}\bar{x}(dt) &= \bar{x}(0) + \sigma_x^2(0)dt + \mathcal{O}(dt^2), \quad \text{or}\\ \frac{\bar{x}(dt) - \bar{x}(0)}{dt} &= \sigma_x^2(0) + \mathcal{O}(dt)\end{aligned}$$

And letting $dt \to 0$ gives:

$$\frac{d\bar{x}}{dt} = \sigma_x^2$$

which is the continuous-time formulation of Fisher's fundamental theorem of natural selection.

1.2 Deterministic dynamics 2: Two-locus model

1.2.1 Change of notation

- Let superscripts $^{(i,j)}$ denote the i^{th} derivative with respect to the first argument and the $j^{(th)}$ derivative with respect to the second argument. For example:

$$\frac{\partial}{\partial\varphi\partial\theta}\Phi(\varphi,\theta) = \Phi^{(1,1)}(\varphi,\theta)$$

- Let $\kappa_{i,j}$ denote the $(i,j)^{th}$ bivariate cumulant, i.e.,

$$\kappa_{i,j} = \Phi^{(i,j)}(\varphi,\theta)\Big|_{\varphi,\theta=0} \ .$$

1.2.2 Evolution of the bivariate distribution of fitnesses

We now suppose that there are two "genes" that determine fitness, such that total fitness is determined by their sum. Letting fitness contributions of the two genes be denoted by x and y, respectively, the total fitness is then simply $x + y$. The extension of the previous one-dimensional *pde* is therefore immediate:

Let $u(x,y,t)$ denote probability density in fitness contributions x and y at time t (i.e., $\int_{x,y} u(x,y,t) = 1$ for all t) for an evolving population. Under selection and mutation, u evolves as:

$$\partial_t u(x,y,t) = (x + y - \bar{x} - \bar{y})u(x,y,t) + U\int_{\gamma,\phi} u(x-\gamma, y-\phi, t)g(\gamma,\phi,t) - Uu(x,y,t)$$

where again U is genomic mutation rate, and $g(\gamma,\phi,t)$ is again the "distribution of fitness effects" of newly-arising mutations, or DFE, only now it is a bivariate distribution.

1.2.3 Evolution of the corresponding characteristic function

Let $\Phi(\varphi,\theta,t)$ denote the characteristic function for $u(x,y,t)$, i.e., $\Phi(\varphi,\theta,t) = \int e^{i\varphi x + i\theta y}u(x,y,t)dxdy$ and let $\mathcal{M}(\varphi,\theta,t)$ denote the characteristic function for the DFE, i.e., $\mathcal{M}(\varphi,\theta,t) = \int e^{i\varphi x + i\theta y}g(x,y,t)dx$. The transformed equation is:

$$\begin{aligned}\Phi^{(0,0,1)}(\varphi,\theta,t) = &- i\Phi^{(1,0,0)}(\varphi,\theta,t) - i\Phi^{(0,1,0)}(\varphi,\theta,t) + [i\Phi^{(1,0,0)}(0,0,t) + i\Phi^{(0,1,0)}(0,0,t)]\Phi(\varphi,\theta,t)\\ &+ U\Phi(\varphi,\theta,t)(\mathcal{M}(\varphi,\theta,t) - 1).\end{aligned}$$

Again, over the time interval in question (assumed to be short on evolutionary time scales), we will suppose

the DFE is invariant such that $\mathcal{M}(\varphi,\theta,t)=\mathcal{M}(\varphi,\theta)$. And letting $\mathcal{C}(\varphi,\theta,t)=\ln\Phi(\varphi,\theta,t)$, we have:

$$\mathcal{C}^{(0,0,1)}(\varphi,\theta,t)=-i\mathcal{C}^{(1,0,0)}(\varphi,\theta,t)-i\mathcal{C}^{(0,1,0)}(\varphi,\theta,t)+i\mathcal{C}^{(1,0,0)}(0,0,t)+i\mathcal{C}^{(0,1,0)}(0,0,t)+U(\mathcal{M}(\varphi,\theta)-1). \quad (5)$$

This equation is a two-dimensional variant of the transport equation and has more possible solution forms than the one-dimensional case, namely, solutions can be of the form: $\mathcal{C}(-it+\varphi,\theta-\varphi)$, $\mathcal{C}(-it+\theta,\varphi-\theta)$, or $\mathcal{C}(-it+\varphi,-it+\theta)$. The solution form that works and that satisfies the boundary condition is the last one. When boundary condition $\mathcal{C}(0,0,t)=0$ is applied, it has solution:

$$\mathcal{C}(\varphi,\theta,t)=\mathcal{C}(\varphi-it,\theta-it,0)-\mathcal{C}(-it,-it,0)-iU\int_{-it}^{0}(\mathcal{M}(\varphi+\gamma,\theta+\gamma)-\mathcal{M}(\gamma,\gamma))d\gamma \quad (6)$$

1.2.4 Dynamics of mean fitness

Rates of change of mean genic fitnesses at the two loci are obtained by taking the derivative of Eq (5) with respect to φ and θ, respectively, and evaluating at $\varphi=\theta=0$. This yields:

$$\begin{aligned}\partial_t\bar{x}(t) &= \sigma_X^2(t)+\sigma_{XY}(t)-U\bar{s}_X\\ \partial_t\bar{y}(t) &= \sigma_Y^2(t)+\sigma_{XY}(t)-U\bar{s}_Y\end{aligned}$$

where $\bar{s}_X$ is mean deleterious effect of mutation at the x-locus, and $\bar{s}_Y$ is mean deleterious effect of mutation at the y-locus. Mean genic fitnesses at time t are obtained by applying the same procedure to Eq (6). Letting $\mathcal{C}(\varphi,\theta):=\mathcal{C}(\varphi,\theta,0)$, this gives a general expression for mean fitness evolution under selection and mutation:

$$\begin{aligned}\bar{x}(t) &= -i\,\mathcal{C}^{(1,0)}(-it,-it)+U[M(-it,-it)-1]\\ \bar{y}(t) &= -i\,\mathcal{C}^{(0,1)}(-it,-it)+U[M(-it,-it)-1]\quad .\end{aligned}$$

1.2.5 Covariance dynamics

The covariance dynamics for the case $U=0$ are given directly by:

$$\sigma_{XY}(t)=\mathcal{C}^{(1,1)}(-it,-it)$$

Now we define the empirical characteristic function at time zero:

$$\tilde{\Phi}(\varphi,\theta)=\frac{1}{N}\sum_{j=1}^{N}e^{iX_j\varphi+iY_j\theta}$$

where X_j and Y_j are measures of genic fitness contribution. And we then define:

$$\tilde{\mathcal{C}}(\varphi,\theta)=\ln\tilde{\Phi}(\varphi,\theta)$$

So that future covariance dynamics are predicted explicitly from empirical data by:

$$\tilde{\sigma}_{XY}(t) = \tilde{\mathcal{C}}^{(1,1)}(-it, -it) \quad .$$

This covariance-forecasting equation is shown to be very accurate in Extended Data Fig. 8.

1.3 Stochastic dynamics: Incorporating genetic drift

For our first few steps, we follow the logic outlined in Ewens' book [3], section 4.10. We use the same notation as in that reference, with the exception of his use of the variable x which we replace with q, because we will later use X as we have before, to denote the fitness contribution of one of the two genes. We define the expectation of some arbitrary function $g(\mathbf{q})$, to be:

$$\mathbb{E}[g(\mathbf{q})] = \int g(\mathbf{q}) f(\mathbf{q}; \mathbf{p}, t) d\mathbf{q}$$

where $f(\mathbf{q}; \mathbf{p}, t)$ is a probability density of a diffusion process in $\mathbf{q}$ with initial frequencies $\mathbf{p}$.

Ewens [3] (p.154, eq.4.83) gives the rate of change of the expectation of $g(\mathbf{q})$:

$$\frac{\partial}{\partial t}\mathbb{E}[g(\mathbf{q})] = \mathbb{E}\left[\sum a_i(\mathbf{q})\frac{\partial g(\mathbf{q})}{\partial q_i} + \frac{1}{2}\sum b_i(\mathbf{q})\frac{\partial^2 g(\mathbf{q})}{\partial q_i^2} + \sum\sum c_{ij}(\mathbf{q})\frac{\partial^2 g(\mathbf{q})}{\partial q_i \partial q_j}\right] \tag{7}$$

We now define the function $g(\mathbf{q})$ to be:

$$g(\mathbf{q}) = g(q_1, q_2, ..., q_n) = \texttt{Log}\left(\sum_{i=1}^{n} q_i e^{\theta X_i + \phi Y_i}\right) \;=\; \tilde{\mathcal{C}}(\theta, \phi) \tag{8}$$

where, adhering to our previous notation, the X_i and Y_i are fitness contributions of the two genes in question, as before, and q_i denotes the frequency of individuals with total fitness $Z_i = X_i + Y_i$.

The first term on the right-hand side of (7) is the selection term, with:

$$a_i(\mathbf{q})dt + \mathcal{O}(\delta t) = \mathbb{E}[\delta q_i] = q_i(Z_i - \mathbb{E}[Z])$$

and the second two terms are drift terms, with:

$$b_i(\mathbf{q})dt + \mathcal{O}(\delta t) = \texttt{Var}[\delta q_i] = q_i(1 - q_i)/n$$

and

$$c_{ij}(\mathbf{q})dt + \mathcal{O}(\delta t) = \texttt{Cov}[\delta q_i, \delta q_j] = -q_i q_j/n$$

Plugging these definitions into Eq. (7), we have:

- First term (selection):

$$\sum_i a_i(\mathbf{q})\frac{\partial g(\mathbf{q})}{\partial q_i} = \frac{\sum_i q_i(X_i+Y_i)e^{\theta X_i+\phi Y_i}}{\sum_i q_i e^{\theta X_i+\phi Y_i}} - \sum_i q_i(X_i+Y_i)$$
$$= \tilde{\mathcal{C}}^{(1,0)}(\theta,\phi) + \tilde{\mathcal{C}}^{(0,1)}(\theta,\phi) - \tilde{\mathcal{C}}^{(1,0)}(0,0) - \tilde{\mathcal{C}}^{(0,1)}(0,0)$$

  as before, where $\tilde{\mathcal{C}}(\theta,\phi) = \tilde{\mathcal{C}}(\theta,\phi,0)$ is the cumulant-generating function associated with random variables X and Y at time zero, as defined above in (8).

- Second term (drift 1):

$$\frac{1}{2}\sum_i b_i(\mathbf{q})\frac{\partial^2 g(\mathbf{q})}{\partial q_i^2} = -\frac{1}{2}\frac{\frac{1}{n}\sum_i q_i(1-q_i)e^{2\theta X_i+2\phi Y_i}}{\left(\sum_i q_i e^{\theta X_i+\phi Y_i}\right)^2}$$

- Third term (drift 2):

$$\sum_i\sum_{j>i} c_{ij}(\mathbf{q})\frac{\partial^2 g(\mathbf{q})}{\partial q_i \partial q_j} = \frac{-\frac{1}{n}\sum_i\sum_{j>i} q_i q_j e^{\theta(X_i+X_j)+\phi(Y_i+Y_j)}}{\left(\sum_i q_i e^{\theta X_i+\phi Y_i}\right)^2}$$

The two drift terms have a common denominator so the numerators can simply be added. When added, it can be rearranged so that the sum of the two drift terms is:

$$\frac{\frac{1}{2}\left(\sum q_i e^{\theta X_i+\phi Y_i}\right)^2 - \frac{1}{2}q_i e^{2\theta X_i+2\phi Y_i}}{\left(\sum q_i e^{\theta X_i+\phi Y_i}\right)^2} = \frac{1}{2n}\frac{\tilde{\Phi}(\theta,\phi)^2 - \tilde{\Phi}(2\theta,2\phi)}{\tilde{\Phi}(\theta,\phi)^2},$$

where $\tilde{\Phi}(\theta,\phi) = \sum_i q_i e^{\theta X_i+\phi Y_i}$, the moment-generating function associated with random variables X and Y. And of course we have that $\tilde{\Phi}(\theta,\phi) = e^{\tilde{\mathcal{C}}(\theta,\phi)}$, so that the drift term may be rewritten as:

$$\frac{1}{2n}\left(1 - e^{\tilde{\mathcal{C}}(2\theta,2\phi)-2\tilde{\mathcal{C}}(\theta,\phi)}\right)$$

So now the whole CGF equation looks like this:

$$\frac{\partial}{\partial t}\mathbb{E}[g(\mathbf{q})] = \frac{\partial}{\partial t}\mathbb{E}[\tilde{\mathcal{C}}(\theta,\phi)] = \mathbb{E}\left[\tilde{\mathcal{C}}^{(1,0)}(\theta,\phi) + \tilde{\mathcal{C}}^{(0,1)}(\theta,\phi) - \tilde{\mathcal{C}}^{(1,0)}(0,0) - \tilde{\mathcal{C}}^{(0,1)}(0,0) + \frac{1}{2n}\left(1 - e^{\tilde{\mathcal{C}}(2\theta,2\phi)-2\tilde{\mathcal{C}}(\theta,\phi)}\right)\right]$$

We suspect this equation can no longer be solved because of the non-local funny business in the drift term (the 2θ and 2ϕ), but we can immediately see how drift affects the covariance by taking derivatives with respect to θ and ϕ and setting these equal to zero:

$$\partial_t \sigma_{XY}(t) = \kappa_{1,2}(t) + \kappa_{2,1}(t) - \frac{1}{n}\sigma_{XY}(t)$$

where $\kappa_{i,j}$(t) is the $(i,j)^{th}$ joint cumulant of X and Y at time t, and we recall $\sigma_{XY}(t) = \kappa_{1,1}(t)$. This shows that drift will tend to weakly push covariance towards zero from either side.

Now writing out the full equation, with selection, mutation, and drift, we have:

$$\partial_t \sigma_{XY}(t) = \kappa_{1,2}(t) + \kappa_{2,1}(t) + U m_{1,1} - \frac{1}{n}\sigma_{XY}(t)$$

where $m_{1,1} = \mathbb{E}(\Delta X \Delta Y)$ and ΔX and ΔY are changes in fitness due to mutation. I.e., $m_{1,1}$ is the first joint moment of the DFE.

In Ewen's book [3], n is interpreted as the number of alleles plus one: $n = K - 1$, where K is the number of alleles. And if you start with an asexual population in which all individuals have different fitnesses, then in effect you have $K = N$ alleles, where N is population size, so that $n = N - 1 \approx N$.

The foregoing developments allow us to study the effects of drift in isolation:

$$\partial_t \sigma_{XY}(t) = -\frac{1}{n}\sigma_{XY}(t) \ ,$$

giving rise to the prediction that under drift only,

$$\sigma_{XY}(t) = \sigma_{XY}(0) e^{-t/n} \quad . \tag{9}$$

We compare these predictions with simulations in Extended Data Fig. 9. Simulations were individual-based and stochastic; they started with a population that was heterogeneous in with $\sigma_{XY}(0) = -0.025$, and proceeded with no selection and no mutation. Results of the simulations support the interpretation of n as N.

1.4 Generalized evolutionary model

Two-loci

We now treat X and Y not as fitness components per se, but as fitness-related phenotypes. In this new formulation, total fitness is $Z = \phi(X, Y)$, where ϕ is any function of X and Y.

We are now effectively in 3 dimensions, and we thus define the following:

- Probability density of individuals having fitness $Z = z$ and fitness-related phenotypes $X = x$ and $Y = y$:

$$u(x, y, z)$$

- Evolution equation without drift:

$$\frac{\partial}{\partial t} u(x, y, z) = (z - \bar{z}) u(x, y, z) + U \int_{\delta_x, \delta_y} g(x - \delta_x, y - \delta_y, z) g(\delta_x, \delta_y) - U$$

- Moment-generating function for $u(x, y, z)$:

$$\Phi(\theta, \phi, \gamma) = \mathbb{E}[e^{\theta X + \phi Y + \gamma Z}]$$

- Cumulant-generating function for $u(x, y, z)$:

$$\mathcal{C}(\theta, \phi, \gamma) = \texttt{Log}\Phi(\theta, \phi, \gamma)$$

- Moment-generating function for DFE $g(\delta_x, \delta_y)$:

$$\mathcal{M}(\theta, \phi) = \mathbb{E}[e^{\theta \Delta X + \phi \Delta Y}]$$

Following steps similar to previous derivations, the evolution equation in cumulant form is now (with drift):

$$\frac{\partial}{\partial t}\mathcal{C}(\theta, \phi, \gamma) = \mathcal{C}_\gamma(\theta, \phi, \gamma) - \mathcal{C}_\gamma(0, 0, 0) + U(\mathcal{G}(\theta, \phi) - 1) + \frac{1}{2N}\left(1 - e^{\mathcal{C}(2\theta, 2\phi, 2\gamma) - 2\mathcal{C}(\theta, \phi, \gamma)}\right) \tag{10}$$

From here, we immediately have:

$$\begin{aligned} \partial_t \bar{x}(t) &= \sigma_{XZ} - U\bar{s}_X \\ \partial_t \bar{y}(t) &= \sigma_{YZ} - U\bar{s}_Y \ , \end{aligned} \tag{11}$$

a restatement of the full Price equation. And dynamics of covariance in X and Y are:

$$\partial_t \kappa_{1,1,0} = \kappa_{1,1,1} + U m_{1,1} - \frac{1}{N}\kappa_{1,1,0} \ ,$$

where the κ are cumulants as before, and $m_{1,1} = \mathbb{E}[\Delta X \Delta Y]$. If we ignore the drift term for now, this may be rewritten as[1]:

$$\frac{\partial}{\partial t}\mathbb{E}[(X - \bar{X})(Y - \bar{Y})] = \mathbb{E}[(X - \bar{X})(Y - \bar{Y})(Z - \bar{Z})] + U\mathbb{E}_g[\Delta X \Delta Y] \ .$$

Fitness functions

As stated above, fitness is $Z = \phi(X, Y)$, where ϕ is some function of fitness-related phenotypes X and Y.

- **Additive**. When $\phi(X, Y) \coloneqq X + Y$, this more general model collapses back into the equations derived from the previous model (intuitively) in which X and Y were considered "additive fitness components" of Z. We have:

$$\sigma_{XZ} = \sigma_{X,X+Y} = \sigma_X^2 + \sigma_{XY} \ ,$$

[1] This can also be written as follows:

$$\partial_t \sigma_{XY} = \sigma_{XYZ} - m_X \sigma_{YZ} - m_Y \sigma_{XZ} - m_Z \sigma_{XY} + U\bar{s}_{xy},$$

where $m_\bullet = \mathbb{E}[\bullet]$, $\sigma_{\bullet,\bullet} = \texttt{Cov}(\bullet, \bullet)$, and $\sigma_{XYZ} \coloneqq \mathbb{E}[XYZ] - \mathbb{E}[X]\mathbb{E}[Y]\mathbb{E}[Z]$.

which, when plugged into Eq (11) yields:

$$\partial_t \bar{x}(t) = \sigma_X^2 + \sigma_{XY} - U\bar{s}_X$$
$$\partial_t \bar{y}(t) = \sigma_Y^2 + \sigma_{XY} - U\bar{s}_Y \ .$$

This gives rise to the previously-derived observation that σ_{XY} may be computed just from data for X. (Or likewise, from data for Y only.)

- **Multiplicative**. Our independent variables are already in log-fitness space (owing to the fact that our model is in continuous time), and it is thus not clear how to interpret a multiplicative model. Were it to have some biological interpretation, however, this is what it looks like:

$$\sigma_{X,Z} = \sigma_{X,XY} \ ,$$

which, when plugged into Eq (11) yields:

$$\partial_t \bar{x}(t) = \sigma_{X,XY} + Um_X \ .$$

We have lost the convenient fact that $\texttt{Cov}(X, Y)$ can be computed with data for X alone, as we had in the additive case, but we do have that $\texttt{Cov}(X, XY)$ can be computed with data for X alone. This is more difficult to interpret, however, and does not nicely translate to a selective advantage for recombination.

- **Gaussian fitness peak**. Here, we assume that $\phi(X, Y) \coloneqq \texttt{Log}\mathcal{N}(\mu, \Sigma)$, where $\mu = (x_p, y_p)$ and $\Sigma = \begin{pmatrix} \sigma_X^2 & \rho\sigma_X\sigma_Y \\ \rho\sigma_X\sigma_Y & \sigma_Y^2 \end{pmatrix}$. We define new variables:

$$\tilde{X} \coloneqq \frac{X - x_p}{\sqrt{2}\ \sigma_X} \quad \text{and} \quad \tilde{Y} \coloneqq \frac{Y - y_p}{\sqrt{2}\ \sigma_Y}$$

where the fitness peak is found at the point (x_p, y_p). Then we have:

$$\texttt{Cov}(X, Z) = (1 - \rho^2)^{-1}\texttt{Cov}(X, -\tilde{X}^2 + 2\rho\tilde{X}\tilde{Y} - \tilde{Y}^2) \ ,$$

where ρ is the correlation coefficient associated with the fitness peak. A positive correlation, for example, would mean that individuals with similar values of X and Y would tend to have higher fitness than individuals with divergent values of X and Y. This equation, when plugged into Eq (11) yields:

$$\frac{\partial}{\partial t}\mathbb{E}[X] = -\texttt{Cov}(\tilde{X}, \tilde{X}^2) + 2\rho\texttt{Cov}(\tilde{X}, \tilde{X}\tilde{Y}) - \texttt{Cov}(\tilde{X}, \tilde{Y}^2) + U\mathbb{E}_g[\Delta X] \ .$$

and for completeness, we write the equation in Y:

$$\frac{\partial}{\partial t}\mathbb{E}[Y] = -\texttt{Cov}(\tilde{Y}, \tilde{Y}^2) + 2\rho\texttt{Cov}(\tilde{Y}, \tilde{X}\tilde{Y}) - \texttt{Cov}(\tilde{Y}, \tilde{X}^2) + U\mathbb{E}_g[\Delta Y] \ .$$

- **First-order expansion of $f(X,Y)$.** If our starting values are $X = x_0$ and $Y = y_0$, then we have:

$$f(X,Y) \approx f(x_0,y_0) + (X - x_0)\partial_x f(x_0,y_0) + (Y - y_0)\partial_y f(x_0,y_0) \ .$$

  We can of course rescale so that $x_0 = y_0 = 0$, giving:

$$f(X,Y) \approx f(0,0) + X\partial_x f(0,0) + Y\partial_y f(0,0) \ .$$

n-loci

Our present work does not yet rely on this case. A subsequent publication will develop this case in greater depth. We only mention in passing that dynamics of means of genic fitnesses is immediate:

$$\frac{\partial}{\partial t}\mathbb{E}[X_i] = \sum_{j=1}^{n} \mathtt{Cov}(X_i, X_j) + U\mathbb{E}_g[\Delta X_i] \ ,$$

which is a continuous-time polygenic version of the full Price equation.

2 Covariance and recombinant advantage

2.1 Classical discrete-time definition of relative fitness

Using standard notation and definitions, we let w_i denote the mean number of offspring that the i^{th} individual contributes to the next generation, and $\bar{w} = \frac{1}{N}\sum_{i=1}^{N} w_i$, the grand mean number of offspring taken across all individuals in the population. The relative fitness of the i^{th} individual is simply:

$$\frac{w_i}{\bar{w}} \tag{12}$$

We emphasize here that this definition of relative fitness is in *discrete time*, where the discrete time interval is a generation. While it makes biological sense and is the most commonly-used definition of relative fitness, technically speaking it implicitly makes the questionable assumption of synchronous reproduction, which can introduce error.

We now suppose that each individual has two genes, having genic fitnesses x and y. In the absence of epistasis, the relative fitness of the i^{th} individual is:

$$\frac{x_i y_i}{\bar{x}\bar{y}} \tag{13}$$

2.2 Recombination

If a recombinant is produced that carries the x allele from the i^{th} individual and the y allele from the j^{th} individual, the relative fitness of the recombinant will be:

$$\frac{x_i y_j}{\bar{x}\bar{y}} \tag{14}$$

If a recombinant is produced that carries the x allele from the i^{th} individual and the y allele from a randomly chosen individual in the population, then on average, the relative fitness of the recombinant will be:

$$\frac{x_i \frac{1}{N}\sum_{j=1}^{N} y_j}{\bar{x}\bar{y}} \tag{15}$$

Following the same logic, if a recombinant is produced from two randomly-chosen parents, then on average, the relative fitness of the recombinant will be:

$$\bar{w}_r = \frac{\frac{1}{N}\sum_{i=1}^{N} x_i \frac{1}{N}\sum_{j=1}^{N} y_j}{\bar{x}\bar{y}} \quad \xrightarrow{N\to\infty} \quad \frac{\mathbb{E}[x]\mathbb{E}[y]}{\mathbb{E}[xy]} \tag{16}$$

2.3 Selective advantage of recombinants

The standard discrete-time definition of selective advantage is mean relative fitness after one generation minus one. By this definition, the mean selective advantage of recombinants is:

$$\bar{s}_r = \bar{w}_r - 1 = \frac{\mathbb{E}[x]\mathbb{E}[y]}{\mathbb{E}[xy]} - 1 = \frac{-\mathtt{Cov}(x,y)}{\bar{w}} \tag{17}$$

where $\bar{w} = \mathbb{E}[xy]$, the mean fitness of the population.

2.4 Log fitness

We now define log-fitnesses, $X = \log x$, and $Y = \log y$, and we rewrite Eq (13) as:

$$\frac{e^{X_i} e^{Y_i}}{\frac{1}{N}\sum_{j=1}^{N} e^{X_j+Y_j}} \tag{18}$$

If a recombinant is produced that carries the X allele from the i^{th} individual and the Y allele from the j^{th} individual, the relative fitness of the recombinant will be:

$$\frac{e^{X_i} e^{Y_j}}{\frac{1}{N}\sum_{j=1}^{N} e^{X_j+Y_j}}$$

If a recombinant is produced that carries the X allele from the i^{th} individual and the Y allele from a randomly chosen individual in the population, then on average, the relative fitness of the recombinant will be:

$$\frac{e^{X_i} \frac{1}{N}\sum_{j=1}^{N} e^{Y_j}}{\frac{1}{N}\sum_{j=1}^{N} e^{X_j+Y_j}}$$

Following the same logic, if a recombinant is produced from two randomly-chosen parents, then on average, the relative fitness of the recombinant will be:

$$\frac{\frac{1}{N}\sum_{i=1}^{N} e^{X_i} \frac{1}{N}\sum_{j=1}^{N} e^{Y_j}}{\frac{1}{N}\sum_{j=1}^{N} e^{X_j+Y_j}} \xrightarrow{N\to\infty} \frac{\mathbb{E}[e^X]\mathbb{E}[e^Y]}{\mathbb{E}[e^{X+Y}]} \tag{19}$$

This defines the mean relative fitness of a randomly-chosen recombinant. The selective advantage of recombinants is now:

$$\bar{s}_r = \bar{w}_r - 1 = \frac{\mathbb{E}[e^X]\mathbb{E}[e^Y]}{\mathbb{E}[e^{X+Y}]} - 1 = \frac{-\mathtt{Cov}(e^X, e^Y)}{\bar{w}} \ ,$$

where here $\bar{w} = \mathbb{E}[e^{X+Y}]$.

2.5 Characteristic function form

If X and Y follow some bivariate distribution whose evolving probability density is $u(x, y, t)$ at time t, then the associated characteristic function (*cf*) at time t is:

$$\Phi_t(\varphi, \theta) = \int_{x,y} e^{i\varphi x + i\theta y} u(x, y, t) \;=\; \mathbb{E}[e^{i\varphi X + i\theta Y}]_t \tag{20}$$

Writing Eq (19) in terms of Eq (20), the mean relative fitness of a randomly-chosen recombinant may now be rewritten in terms of *cf*'s as:

$$\bar{w}_r(t) \;=\; \frac{\Phi_t(-i, 0)\Phi_t(0, -i)}{\Phi_t(-i, -i)}$$

2.6 Cumulant-generating function form

The cumulant-generating function (*cgf*) is simply the log of the *cf*; thus we define:

$$\mathcal{C}_t(\varphi, \theta) = \log \Phi_t(\varphi, \theta) \tag{21}$$

from which the mean relative fitness of a randomly-chosen recombinant at time t, may now be rewritten in terms of *cgf*'s as:

$$\bar{w}_r(t) \;=\; \frac{e^{\mathcal{C}_t(-i,0) + \mathcal{C}_t(0,-i)}}{e^{\mathcal{C}_t(-i,-i)}} \;=\; e^{\mathcal{C}_t(-i,0) + \mathcal{C}_t(0,-i) - \mathcal{C}_t(-i,-i)} \tag{22}$$

We are now prepared to derive the evolution over time of the relative fitness of recombinants. But first, a few observations are in order:

- While equations (20) and (21) are expressed in terms of a continuous distribution $f(x, y)$, there are data-friendly discrete versions of both, which we present below. These discrete versions make no assumptions about the *resolution* of the fitness data, and work even when fitnesses are very granular with only a few fitness types in the population.

2.7 Dynamics of recombinant fitness

In section 1.2, we derived the time evolution of the *cgf* for genic fitness X and Y. Here, we rewrite the "selection-only" version of *cgf* dynamics:

$$\mathcal{C}_t(\varphi, \theta) = \mathcal{C}(\varphi - it, \theta - it) - \mathcal{C}(-it, -it) \tag{23}$$

where $\mathcal{C}(\varphi, \theta) \coloneqq \mathcal{C}_0(\varphi, \theta)$ the *cgf* at time zero. Now, we are armed and ready to write down the time evolution of recombinant fitness. Applying Eq (23) to the terms in Eq (22) we have:

- $\mathcal{C}_t(-i, 0) = \mathcal{C}(1 - it, -it) - \mathcal{C}(-it, -it)$
- $\mathcal{C}_t(0, -i) = \mathcal{C}(-it, 1 - it) - \mathcal{C}(-it, -it)$
- $\mathcal{C}_t(-i, -i) = \mathcal{C}(1 - it, 1 - it) - \mathcal{C}(-it, -it)$

Substituting these expressions into Eq (22) gives recombinant relative fitness as a function of time:

$$w_r(t) \;=\; e^{\mathcal{C}(1-it,-it)+\mathcal{C}(-it,1-it)-\mathcal{C}(1-it,1-it)-\mathcal{C}(-it,-it)} \tag{24}$$

This expression forecasts the time evolution of recombinant relative fitness, given only the fitness distribution at time zero; that is, all that is needed is the initial *cgf*, $\mathcal{C}(\varphi,\theta)$.

Interpretation of Eq (24) : Equation (24) gives a classical discrete-time relative fitness of recombinants, and yet it employs Eq (21) which derives from a continuous time model. The correct interpretation of Eq (24) is that it gives the mean relative fitness of recombinants, where fitness is defined in the classical per-generation sense, but it does so continuously. For example, its prediction for fitness at time $t = 23.7$ is correctly interpreted as a relative change in mean offspring number between times $t = 23.7$ and $t = 24.7$.

2.8 How to get the *cgf* from data in a finite population

We suppose we have a set of empirically-determined genic fitness values for X and Y, say X_i and Y_i for $i = 1, 2, ..., n$. We can employ an empirical version of Eq (21):

$$\hat{\mathcal{C}}(\varphi,\theta) = \log \frac{1}{N}\sum_{i=1}^{N} e^{i\varphi X_i + i\theta Y_i} \tag{25}$$

to forecast the evolution of recombinant fitness, by substituting $\hat{\mathcal{C}}$ for $\mathcal{C}$ in Eq (24).

While this formula can be used to compute the *cgf* from real data, here we use it for a different purpose, namely, to compute expectations for finite populations.

For example, the expected dynamics of recombinant fitness, $\mathbb{E}[w_r(t)]$, in a finite population of size N, can be obtained by replacing $\mathcal{C}$ in Eq (24) with $\hat{\mathcal{C}}$ from Eq (25), and integrating over random variables X_i and Y_i.

2.9 An alternative derivation of the covariance result with classical population-genetic definitions as the starting point

Equation (24) is built from the classical definition of relative fitness. We now expand each term of the exponent in (24):

- $\mathcal{C}(1-it,-it) = \mathcal{C}(-it,-it) + \mathcal{C}^{(1,0)}(-it,-it) + \frac{1}{2}\mathcal{C}^{(2,0)}(-it,-it) + \mathcal{O}(\mathcal{C}^{(3,0)}(-it,-it))$
- $\mathcal{C}(-it,1-it) = \mathcal{C}(-it,-it) + \mathcal{C}^{(0,1)}(-it,-it) + \frac{1}{2}\mathcal{C}^{(0,2)}(-it,-it) + \mathcal{O}(\mathcal{C}^{(0,3)}(-it,-it))$
- $\mathcal{C}(1-it,1-it) = \mathcal{C}(-it,-it) + \mathcal{C}^{(1,0)}(-it,-it) + \mathcal{C}^{(0,1)}(-it,-it)$
  $+ \frac{1}{2}\left(\mathcal{C}^{(0,2)}(-it,-it) + 2\mathcal{C}^{(1,1)}(-it,-it) + \mathcal{C}^{(2,0)}(-it,-it)\right) + \mathcal{O}(\mathcal{C}^{(i,j)}(t,t)|_{i+j=3})$

and we substitute these expansions back into Eq (24); this reduces to the following compact expression for the dynamics of recombinant fitness:

$$\bar{w}_r(t) = e^{-\mathcal{C}^{(1,1)}(-it,-it)} \tag{26}$$

This expression is identical to the expression for recombinant fitness derived from our Fourier-transform approach. Curiously, the expression derived from the Fourier-transform is exact, whereas here Taylor series truncations are required. We note, however, that this approach is exact when fitness is gaussian, because in this case all of the $\mathcal{O}(\cdot)$ terms are identically zero, such that the series truncations are exact.

2.10 Covariance and recombinant advantage in continuous time

We define:

- $\mathbb{E}[X+Y]_t$ is expected wildtype fitness at time t.
- $\mathbb{E}_r[X+Y]_t$ is expected recombinant fitness at time t.
- $\bar{s}_r(t)$ is the mean selective advantage of recombinants at time t:

$$\bar{s}_r(t) = \mathbb{E}_r[X+Y]_t - \mathbb{E}[X+Y]_t$$

We have:

$$\bar{s}_r(0) = \mathbb{E}_r[X+Y]_0 - \mathbb{E}[X+Y]_0 = 0$$

and will show that, if $\sigma_{XY} < 0$ then:

$$\bar{s}_r(t>0) = \mathbb{E}_r[X+Y]_{t>0} - \mathbb{E}[X+Y]_{t>0} > 0$$

After one generation, we have:

$$\begin{aligned}\bar{s}_r(1) &\approx \bar{s}_r(0) + \partial_t \bar{s}_r(0) = \partial_t \bar{s}_r(0) \\ &= \partial_t \mathbb{E}_r[X+Y]_0 - \partial_t \mathbb{E}[X+Y]_0\end{aligned}$$

where:

$$\begin{aligned}\partial_t \mathbb{E}_r[X+Y]_0 &= \sigma_X^2 + \sigma_Y^2 \\ \partial_t \mathbb{E}[X+Y]_0 &= \sigma_X^2 + \sigma_Y^2 + 2\sigma_{XY}\end{aligned}$$

so that:

$$s_R(1) \approx -2\sigma_{XY}$$

Employing a Moran model of evolution, we find that recombinant advantage increases linearly from 0 to $-2\sigma_{XY}$ over the course of a single generation (Extended Data Fig. 1), such that the averaged recombinant advantage during that first generation is:

$$\bar{\bar{s}}_r = -\sigma_{XY}$$

3 The *products* of natural selection promote recombination

3.1 General setting: m loci, n genotypes

Let n and m be two positive integers. Let $(X_{i,j})_{1\leqslant i\leqslant n;1\leqslant j\leqslant m}$ be a rectangular array of independent random variables. For our purposes, each X quantifies a fitness-related phenotype encoded at one locus. Each row represents an individual's haploid genome and each column represents a locus on that genome. See Extended Data Fig. 10. We shall denote by $X_{(1)} = (X_{i,j})_{1\leqslant j\leqslant m}$ the i-th row of the array (the i-th individual in a population). Let ϕ be a measurable function from $\mathbb{R}^m$ into $\mathbb{R}$. For $i = 1, \ldots, n$, denote by $Z^{[1]}$ the image by ϕ of the i-th row of the array.

$$Z^{[1]} = \phi(X_{(1)}) \, .$$

$Z^{[1]}$ represents the total fitness of individual i. Denote by $\sigma \in \mathcal{S}_n$ the random permutation such that

$$\min_{i=1}^{n} Z^{[1]} = S_{\sigma(1)} \leqslant \cdots \leqslant S_{\sigma(n)} = \max_{i=1}^{n} Z^{[1]} \, .$$

The permutation σ is uniquely defined up to the usual convention of increasing order for indices corresponding to ties. Deterministically, natural selection will cause the genome of highest fitness ($S_{\sigma(n)} = \max_{i=1}^{n} Z^{[1]}$) to fix. We are interested in the statistical properties of the $X_{\sigma(n),j}$; in particular, we are interested in any associations that might arise across loci (across different values of j) in this winning genotype. If these associations are negative, recombination – which alleviates negative associations across loci – should be favored.

For $1 \leqslant i \leqslant n$ and $1 \leqslant j \leqslant m$, define:

$$A_{i,j} = X_{\sigma(i),j} \, .$$

For $1 \leqslant i \leqslant n$, $A_i = (A_{i,j})_{1\leqslant j\leqslant m}$ is that row in the array $(X_{i,j})$ which ranks i-th in the order of images by ϕ.

3.1.1 Density

Proposition 0. *Assume that for $j = 1, \ldots, m$, $X_{i,j}$ has pdf f_j, for all $i = 1, \ldots, n$. Denote by H the common cdf of $Z^{[1]}$'s and assume that H is continuous over its support. The joint pdf of A_i is:*

$$n\, f_1(x_1) \cdots f_m(x_m) \binom{n-1}{i-1} H^{i-1}(\phi(x_1, \ldots, x_m))(1 - H(\phi(x_1, \ldots, x_m)))^{n-i} \, .$$

Proof. For any continous bounded function Ψ of m variables:

$$\begin{aligned} \mathbb{E}(\Psi(A_i)) &= \sum_{\ell=1}^{n} \frac{1}{n} \mathbb{E}(\Psi(X_\ell) \,|\, \sigma(i) = \ell) \\ &= \mathbb{E}(\Psi(X_1) \,|\, \sigma(i) = 1) \, . \end{aligned}$$

Thus the distribution of A_i and the conditional distribution of X_1 given that $\Phi(X_1)$ ranks i-th, are the same. The pdf of X_1 is $f_1(x_1) \cdots f_m(x_m)$. The probability of the event $\sigma(i) = 1$ is $1/n$. Conditioning on $X_1 = (x_1, \ldots, x_m)$, the probability that X_1 ranks i-th is the probability that among $S_2, \ldots, S_n$, $i-1$ are below

$\phi(x_1,\ldots,x_m)$ and $n-i$ are above. The probability for S_ℓ to be below $\phi(x_1,\ldots,x_m)$ is $H(\phi(x_1,\ldots,x_m))$. Hence the result. □

Observe that the average of the densities of A_i's is the common density of all $X_{(1)}$'s, *i.e.* $f_1(x_1),\ldots,f_m(x_m)$. This was to be expected, since choosing at random one of the A_i's is equivalent to choosing at random one of the $X_{(1)}$'s. The question is whether the A_i's are negatively associated in the sense of Joag-Dev and Proschan [7]; this seems a reasonable conjecture in light of Theorems 2.8 and also examples (b) and (c) of section 3.2 in that reference. However we have not been able to prove it. We now focus on the simplest possible scenario:

3.2 Two loci, two genotypes

No hypothesis on the ranking function ϕ is made at this point, apart from being measurable. Notations will be simplified as follows: (X_1,Y_1,X_2,Y_2) are i.i.d.; $(X_{(1)},Y_{(1)})$ (the *infimum*) denotes that couple (X_1,Y_1) or (X_2,Y_2) whose value by ϕ is minimal; $(X_{(2)},Y_{(2)})$ (the *supremum*) denotes that couple (X_1,Y_1) or (X_2,Y_2) whose value by ϕ is maximal.

PROPOSITION 1. *Let ψ be any measurable function from $\mathbb{R}^2$ into $\mathbb{R}$. Then:* $\frac{1}{2}\mathbb{E}(\psi(X_{(1)},Y_{(1)}))+\frac{1}{2}\mathbb{E}(\psi(X_{(2)},Y_{(2)})) = \mathbb{E}(\psi(X_1,Y_1))$. *In particular, the arithmetic mean of $\mathbb{E}(X_{(1)})$ and $\mathbb{E}(X_{(2)})$ is $\mathbb{E}(X_1)$.*

Proof. Consider a random index I, equal to "(1)" or "(2)" each with probability 1/2, independent from (X_1,Y_1,X_2,Y_2). By an argument used in the previous section, the couple (X_I,Y_I) is distributed as (X_1,Y_1). Hence, $\mathbb{E}(\psi(X_I,Y_I)) = \mathbb{E}(\psi(X_1,Y_1))$, however,

$$\begin{aligned}\mathbb{E}(\psi(X_I,Y_I)) &= \mathbb{E}(\mathbb{E}(\psi(X_I,Y_I)\,|\,I)) \\ &= \frac{1}{2}\mathbb{E}(\psi(X_{(1)},Y_{(1)})) + \frac{1}{2}\mathbb{E}(\psi(X_{(2)},Y_{(2)}))\ .\end{aligned}$$

□

PROPOSITION 2. *We have:* $\mathrm{Cov}(X_{(1)},Y_{(1)}) + \mathrm{Cov}(X_{(2)},Y_{(2)}) = -(\mathrm{Cov}(X_{(1)},Y_{(2)}) + \mathrm{Cov}(X_{(2)},Y_{(1)})) = -\frac{1}{2}\mathbb{E}(X_{(2)}-X_{(1)})\mathbb{E}(Y_{(2)}-Y_{(1)})$.

Proof. Consider again the same random index I, equal to "(1)" or "(2)" each with probability 1/2, independent from (X_1,Y_1,X_2,Y_2). The couples (X_I,Y_I) and (X_I,Y_{3-I}) are both distributed as (X_1,Y_1). Therefore their covariances are null. These covariances can also be computed by conditioning on I (see *e.g.* formula (1.1) in [7]). For (X_I,Y_I): $\mathrm{Cov}(X_I,Y_I) = \mathbb{E}(\mathrm{Cov}(X_I,Y_I|I)) + \mathrm{Cov}(\mathbb{E}(X_I|I),\mathbb{E}(Y_I|I))$. On the right-hand side, the first term is: $\mathbb{E}(\mathrm{Cov}(X_I,Y_I|I)) = \frac{1}{2}\mathrm{Cov}(X_{(1)},Y_{(1)}) + \frac{1}{2}\mathrm{Cov}(X_{(2)},Y_{(2)})$. The second term is: $\mathrm{Cov}(\mathbb{E}(X_I|I),\mathbb{E}(Y_I|I)) = \frac{1}{4}\mathbb{E}(X_{(2)}-X_{(1)})\mathbb{E}(Y_{(2)}-Y_{(1)})$. Similarly, we have: $\mathrm{Cov}(X_I,Y_{3-I}) = \mathbb{E}(\mathrm{Cov}(X_I,Y_{3-I}|I))+\mathrm{Cov}(\mathbb{E}(X_I|I),\mathbb{E}(Y_{3-I}|I))$. The first term in the right-hand side is: $\mathbb{E}(\mathrm{Cov}(X_I,Y_{3-I}|I)) = \frac{1}{2}\mathrm{Cov}(X_{(1)},Y_{(2)}) + \frac{1}{2}\mathrm{Cov}(X_{(2)},Y_{(1)})$. The second term in the right-hand side is: $\mathrm{Cov}(\mathbb{E}(X_I|I),\mathbb{E}(Y_{3-I}|I)) = -\frac{1}{4}\mathbb{E}(X_{(2)}-X_{(1)})\mathbb{E}(Y_{(2)}-Y_{(1)})$. Hence the result. □

PROPOSITION 3. *Assume that the ranking function ϕ is symmetric: $\phi(x,y) = \phi(y,x)$. Then the couple $(X_{(1)}, Y_{(2)})$ has the same distribution as the couple $(Y_{(1)}, X_{(2)})$.*

As a consequence, $X_{(1)}$ and $Y_{(1)}$ have the same distribution, so do $X_{(2)}$ and $Y_{(2)}$. Thus: $\mathbb{E}(X_{(2)} - X_{(1)}) = \mathbb{E}(Y_{(2)} - Y_{(1)}) = \frac{1}{2}\mathbb{E}(Z^{[2]} - Z^{[1]})$. Another consequence is that: $\mathrm{Cov}(X_{(1)}, Y_{(2)}) = \mathrm{Cov}(X_{(2)}, Y_{(1)})$. Thus by Proposition 2: $\mathrm{Cov}(X_{(1)}, Y_{(2)}) = \mathrm{Cov}(X_{(2)}, Y_{(1)}) = \frac{1}{16}\mathbb{E}^2(Z^{[2]} - Z^{[1]})$.

Proof. Since ϕ is symmetric, the change of variable $(X_1, Y_1, X_2, Y_2) \mapsto (Y_1, X_1, Y_2, X_2)$ leaves unchanged the couple (S_1, S_2). □

PROPOSITION 4. *Assume that the ranking function ϕ is the sum: $\phi(x,y) = x + y$. Then: $\mathbb{E}(X_{(1)}) = \mathbb{E}(Y_{(1)})$, $\mathbb{E}(X_{(2)}) = \mathbb{E}(Y_{(2)})$, and $\mathbb{E}(X_{(1)}) < \mathbb{E}(X_{(2)})$.*

Proof. The first two equalities come from Proposition 3. By definition, $\mathbb{E}(X_{(1)} + Y_{(1)}) < \mathbb{E}(X_{(2)} + Y_{(2)})$. Hence the inequality. □

PROPOSITION 5. *Assume that the ranking function ϕ is the sum, and that the common distribution of X_1, Y_1, X_2, Y_2 is symmetric: there exists a such that $f(x-a) = f(a-x)$. Then $(a - X_{(1)}, a - Y_{(1)})$ has the same distribution as $(X_{(2)} - a, Y_{(2)} - a)$.*

As a consequence, $\mathrm{Cov}(X_{(1)}, Y_{(1)}) = \mathrm{Cov}(\mathrm{X}_{(2)}, \mathrm{Y}_{(2)})$.

Proof. The change of variable $(X_1, Y_1, X_2, Y_2) \mapsto (2a - X_1, 2a - Y_1, 2a - X_2, 2a - Y_2)$ leaves the distribution unchanged. It only swaps the indices i and s of minimal and maximal sum. □

If we summarize Propositions 1, 2, 3, 4, 5 for the case where the ranking function is the sum, and the distribution is symmetric, one gets:

$$\begin{aligned} \mathrm{Cov}(X_{(1)}, Y_{(1)}) &= \mathrm{Cov}(X_{(2)}, Y_{(2)}) < 0 \\ \mathrm{Cov}(X_{(1)}, Y_{(2)}) &= \mathrm{Cov}(X_{(2)}, Y_{(1)}) > 0 \\ |\mathrm{Cov}(X_{(1)}, Y_{(1)})| &= \mathrm{Cov}(X_{(1)}, Y_{(2)}) = \frac{1}{16}\mathbb{E}^2(Z^{[2]} - Z^{[1]}) \, . \end{aligned}$$

4 The *process* of natural selection promotes recombination

4.1 Two loci, two genotypes

4.1.1 Dynamics of partitioned covariance:

We let $p(t)$ and $q(t) = 1 - p(t)$ denote the frequencies of superior and inferior genotypes, respectively, in a large population at time t. These frequencies are functions of genic fitnesses and are thus dependent on the vector (X_1, Y_1, X_2, Y_2). We define:

$$\mathbf{p}(t) := p(t|X_1, Y_1, X_2, Y_2)$$

and

$$\mathbf{q}(t) := q(t|X_1, Y_1, X_2, Y_2)$$

If the population at time zero consists of half superior and half inferior genotypes, then we know from developments elsewhere that:

$$p(t|X_1, Y_1, X_2, Y_2) = \frac{e^{Z^{[2]}t}}{e^{Z^{[1]}t} + e^{Z^{[2]}t}}$$

and

$$q(t|X_1, Y_1, X_2, Y_2) = \frac{e^{Z^{[1]}t}}{e^{Z^{[1]}t} + e^{Z^{[2]}t}}$$

Dynamics of *total covariance* are:

$$\begin{aligned} \sigma^*_{XY}(t) &= \mathbb{E}[\mathbf{p}(t)X_{(2)}Y_{(2)} + \mathbf{q}(t)X_{(1)}Y_{(1)}] - \mathbb{E}[\mathbf{p}(t)X_{(2)} + \mathbf{q}(t)X_{(1)}]\mathbb{E}[\mathbf{p}(t)Y_{(2)} + \mathbf{q}(t)Y_{(1)}] \\ &\xrightarrow{t\to\infty} \quad \texttt{Cov}(X_{(2)}, Y_{(2)}) \quad = \quad -\frac{1}{16}\mathbb{E}^2[Z^{[2]} - Z^{[1]}] \end{aligned} \tag{27}$$

If the (X_1, Y_1, X_2, Y_2) are *iid* normal, then:

$$\sigma^*_{XY}(t) \xrightarrow{t\to\infty} \frac{\sigma^2_X\sigma^2_Y(\beta_2 - 1)}{\sigma^2_X + \sigma^2_Y}$$

Dynamics of *within-population* covariance are:

$$\sigma_{XY}(t) = \mathbb{E}[\mathbf{p}(t)\mathbf{q}(t)(X_{(2)} - X_{(1)})(Y_{(2)} - Y_{(1)})] \quad \xrightarrow{t\to\infty} \quad 0 \tag{28}$$

Across-population covariance dynamics are:

$$\sigma^a_{XY}(t) = \mathbb{E}[(\mathbf{p}(t)X_{(2)} + \mathbf{q}(t)X_{(1)})(\mathbf{p}(t)Y_{(2)} + \mathbf{q}(t)Y_{(1)})] \tag{29}$$

$$- \quad \mathbb{E}[\mathbf{p}(t)X_{(2)} + \mathbf{q}(t)X_{(1)}]\mathbb{E}[\mathbf{p}(t)Y_{(2)} + \mathbf{q}(t)Y_{(1)}] \tag{30}$$

$$\xrightarrow{t\to\infty} \quad \texttt{Cov}(X_{(2)}, Y_{(2)}) \quad = \quad -\frac{1}{16}\mathbb{E}^2[Z^{[2]} - Z^{[1]}]$$

If the (X_1, Y_1, X_2, Y_2) are *iid* normal, then:

$$\sigma^a_{XY}(t),\ \sigma^*_{XY}(t) \xrightarrow{t\to\infty} \frac{\sigma^2_X\sigma^2_Y(\beta_2 - 1)}{\sigma^2_X + \sigma^2_Y}$$

4.2 Time-integrated covariance: a measure of total recombinant advantage

As we have shown in Section 2, and more specifically in Subsection 2.10, covariance times minus one equals immediate recombinant advantage, where "immediate" is more precisely defined as the advantage that builds over the first generation of growth. Here we derive the time-integral of covariance *within* an evolving population as a measure of total recombinant advantage within that population: If time-integrated covariance is positive, this implies that on average natural selection creates conditions that oppose recombination within the evolving population. On the other hand, if time-integrated covariance is negative, this implies that

natural selection creates conditions that favor recombination within the evolving population, and the more strongly negative the time-integrated covariance, the more advantageous recombinants are.

PROPOSITION 6. *Within-population covariance integrated over time is:*

$$\begin{aligned}\int_0^\infty \sigma_{XY}(t)dt &= \int_0^\infty \mathbb{E}[\mathbf{p}(t)\mathbf{q}(t)(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})]dt \\ &= (1-p)\mathbb{E}[\frac{(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})}{(Z^{[2]}-Z^{[1]})}] \\ &= (1-p)\mathbb{E}[\frac{(X_2-X_1)(Y_2-Y_1)}{|Z_2-Z_1|}] \end{aligned} \tag{31}$$

where p is the initial frequency of the superior genotype.

We note that the integrand, within-population covariance, is immediate (it can be written down from first principles or derived from our *pde* approach) and does not rely on any assumptions about the parent distribution from which fitnesses are drawn. This fact allows us to implement any distribution, as we do in Extended Data Fig. 2.

Proof. We let p denote initial frequency of the superior of the two genotypes, and we let $q = 1-p$ denote initial frequency of the inferior genotype. The dynamic equation for within-population covariance may be written out as:

$$\sigma_{XY}(t) = \frac{pq\mathrm{e}^{(Z^{[1]}+Z^{[2]})t}}{\left(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t}\right)^2}(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})$$

and the time-integral of covariance is:

$$\int_0^\infty \sigma_{XY}(t)dt = (X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})\int_0^\infty \frac{pq\mathrm{e}^{(Z^{[1]}+Z^{[2]})t}}{\left(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t}\right)^2}dt$$

We focus our attention on the integral in the right-hand side. We will show that:

$$\int_0^\infty \frac{pq\mathrm{e}^{(Z^{[1]}+Z^{[2]})t}}{\left(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t}\right)^2}dt = \frac{q}{Z^{[2]}-Z^{[1]}},$$

hence giving Eq (31). We can expand the integrand as follows:

$$\frac{pq\mathrm{e}^{(Z^{[1]}+Z^{[2]})t}}{(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t})^2} = \frac{q}{Z^{[2]}-Z^{[1]}}\left(\frac{(pZ^{[2]}\mathrm{e}^{Z^{[2]}t}+qZ^{[1]}\mathrm{e}^{Z^{[1]}t})\mathrm{e}^{Z^{[1]}t}}{(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t})^2}-\frac{Z^{[1]}\mathrm{e}^{Z^{[1]}t}}{p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t}}\right) \tag{32}$$

We now define:

$$f := \mathrm{e}^{Z^{[1]}t} \quad \text{and} \quad g := \frac{-1}{p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t}}$$

so that:

$$f' = Z^{[1]}\mathrm{e}^{Z^{[1]}t} \quad \text{and} \quad g' = \frac{pZ^{[2]}\mathrm{e}^{Z^{[2]}t}+qZ^{[1]}\mathrm{e}^{Z^{[1]}t}}{(p\mathrm{e}^{Z^{[2]}t}+q\mathrm{e}^{Z^{[1]}t})^2}$$

where the prime indicates derivative with respect to t. We note that the terms inside the parentheses in Eq (32) are fg' and $f'g$. We know from the product rule (integration by parts) that

$$\int fg' + \int f'g = fg$$

so that the integral over time of everything inside the parentheses in Eq (32) reduces to:

$$fg \;=\; \frac{-\mathrm{e}^{Z^{[1]}t}}{p\mathrm{e}^{Z^{[2]}t} + q\mathrm{e}^{Z^{[1]}t}}\Bigg|_{t=0}^{\infty} \;=\; 0-(-1) \;=\; 1$$

Hence the result:

$$\int_0^\infty \frac{pq\mathrm{e}^{(Z^{[1]}+Z^{[2]})t}}{\left(p\mathrm{e}^{Z^{[2]}t} + q\mathrm{e}^{Z^{[1]}t}\right)^2}dt \;=\; \frac{q}{Z^{[2]}-Z^{[1]}}\;,$$

so that:

$$\int_0^\infty \sigma_{XY}(t)dt = q\mathbb{E}[\frac{(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})}{Z^{[2]}-Z^{[1]}}]$$

where q in Prop 6 is written as $1-p$.

We observe that

$$(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)}) = (X_{(1)}-X_{(2)})(Y_{(1)}-Y_{(2)}) = (X_2-X_1)(Y_2-Y_1)$$

and that

$$Z^{[2]}-Z^{[1]} = |Z_2-Z_1|$$

from which we have:

$$\mathbb{E}[\frac{(X_{(2)}-X_{(1)})(Y_{(2)}-Y_{(1)})}{Z^{[2]}-Z^{[1]}}] = \mathbb{E}[\frac{(X_2-X_1)(Y_2-Y_1)}{|Z_2-Z_1|}]$$

□

PROPOSITION 7. *We define spacings $\Delta X = X_2 - X_1$, $\Delta Y = Y_2 - Y_1$, and $\Delta Z = Z_2 - Z_1 = \Delta X + \Delta Y$. If the pairs (X_i, Y_i) are independently drawn from a given distribution, then ΔX and ΔY are symmetric about zero. Moreover, if $\mathbb{E}[\sqrt{|\Delta X \Delta Y|}] < \infty$, then*

$$\int_0^\infty \sigma_{XY}(t)dt \;=\; \mathbb{E}\left[\frac{\Delta X \Delta Y}{|\Delta Z|}\right] \;\leq\; 0.$$

Proof: The fact that $(\Delta X, \Delta Y)$ is symmetric about zero is a direct consequence of the fact that (X_1, Y_1) and (X_2, Y_2) are independent and have the same distribution. Note that, since $|x| + |y| \geq 2\sqrt{|xy|}$ for all $x, y \in \mathbb{R}$, we have

$$\mathbb{E}\left[\mathbb{1}_{\Delta X \Delta Y > 0}\frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right] \leq \frac{1}{2}\mathbb{E}[\sqrt{|\Delta X \Delta Y|}] < \infty.$$

Hence, $\mathbb{E}\left[\Delta X \Delta Y / |\Delta X + \Delta Y|\right]$ is well-defined and given by

$$\mathbb{E}\left[\frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right] = \mathbb{E}\left[\mathbb{1}_{\Delta X \Delta Y > 0} \frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right] + \mathbb{E}\left[\mathbb{1}_{\Delta X \Delta Y < 0} \frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right],$$

where, on the right-hand side, the first term is positive and finite and the second term is negative. If the latter is $-\infty$, the resut follows; if it is finite, since $(-\Delta X, \Delta Y)$ has the same distribution as $(\Delta X, \Delta Y)$, then

$$\begin{aligned}\mathbb{E}\left[\frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right] &= \mathbb{E}\left[\mathbb{1}_{\Delta X \Delta Y > 0} \frac{\Delta X \Delta Y}{|\Delta X + \Delta Y|}\right] + \mathbb{E}\left[\mathbb{1}_{(-\Delta X)\Delta Y < 0} \frac{(-\Delta X)\Delta Y}{|\Delta Y - \Delta X|}\right] \\ &= \mathbb{E}\left[\mathbb{1}_{\Delta X \Delta Y > 0} \Delta X \Delta Y \left(\frac{1}{|\Delta X + \Delta Y|} - \frac{1}{|\Delta Y - \Delta X|}\right)\right].\end{aligned}$$

Since for x and y having the same sign, we have $|x+y| > |y-x|$, the right-hand side in the previous sequence of identities is less than or equal to zero, which concludes the proof. □

Remark: The same proof works for the generalized linear fitness function $\phi(X, Y) = a + bX + cY$ with $b, c > 0$. Note also that the proof tell us that $\mathbb{E}[\Delta X \Delta Y / |\Delta Z|] = 0$ if and only if $\mathbb{P}(\Delta X \Delta Y = 0) = 1$.

Corollary 1. *For any real number κ, let us consider a fitness function of the form $\phi_\kappa(x, y) = a + bX + cY + \kappa g(X, Y)$, where $b, c > 0$ and g is a function independent of κ. Let $Z(\kappa) = \phi_\kappa(X_2, Y_2) - \phi_\kappa(X_1, Y_1)$. Assume that for some $\varepsilon > 0$,*

$$\mathbb{E}\left[\sup_{|\kappa| < \varepsilon} \frac{|\Delta X \Delta Y|}{|Z(\kappa)|}\right] < \infty, \tag{33}$$

and that $\mathbb{P}(\Delta X \Delta Y = 0) < 1$. Then, there is $\varepsilon_0 \in (0, \varepsilon)$, such that for all $\kappa \in (-\varepsilon_0, \varepsilon_0)$, we have

$$\mathbb{E}\left[\frac{\Delta X \Delta Y}{|Z(\kappa)|}\right] < 0.$$

Proof: Condition (33) implies that the function $h : (-\varepsilon, \varepsilon) \to \mathbb{R}$ defined via

$$h(\kappa) = \mathbb{E}\left[\frac{\Delta X \Delta Y}{|Z(\kappa)|}\right]$$

is continuous. Moreover, since $\mathbb{P}(\Delta X \Delta Y = 0) < 1$, proceeding as in the proof of Proposition 7, we obtain that $h(0) < 0$. Hence, by continuity of h, we infer that there is $\varepsilon_0 \in (0, \varepsilon)$ such that h is negative in $(-\varepsilon_0, \varepsilon_0)$, which concludes the proof. □

Let us now focus our attention on the fitness function $\phi_\kappa(X, Y) = aX + bY + \kappa XY$ with $a, b > 0$ and $\kappa \in \mathbb{R}$. As before, let $Z(\kappa) = \phi_\kappa(X_2, Y_2) - \phi_\kappa(X_1, Y_1) = (a + \kappa Y_1)\Delta X + (b + \kappa X_2)\Delta Y$. The case where the random variables $(|\Delta X \Delta Y| / |Z(\kappa)|)_{\kappa \in (-\varepsilon, \varepsilon)}$ are uniformly integrable (i.e. condition (33) is satisfied) is covered already by Corollary 1. As a counterpart, the next result considers the case where the expectation of

$|\Delta X \Delta Y|/|Z(\kappa)|$ is infinite, and provides a simple condition to assure that the expectation of $\Delta X \Delta Y/|Z(\kappa)|$ is negative (in fact, equal to $-\infty$).

Remark: This corollary tells us that Prop 7 holds in the presence of a certain amount of epistasis (the degree depends on the fitness function ϕ) and that, significantly, the interval that constrains the epistatic parameter always contains, and is centered about, zero. The implication is that additive effects are the driving force in creating conditions that favour recombination. The reasons for this fact can be intuited by the following heuristic argument:

Time-integrated covariance $\int_0^\infty \sigma_{X,Y}(t)dt = \mathbb{E}[\frac{\Delta X \Delta Y}{|\Delta Z|}]$ is dominated by what happens when $|\Delta Z|$ is small. A first order expansion of ϕ,

$$Z_2 = \phi(X_2, Y_2) \approx \phi(X_1, Y_1) + \Delta X \partial_x \phi(X_1, Y_1) + \Delta Y \partial_y \phi(X_1, Y_1)$$

becomes increasingly accurate as $|\Delta Z|$ becomes smaller. We note that $\phi(X_1, Y_1) = Z_1$ and we can thus rewrite the expansion as:

$$\Delta Z \approx \Delta X \partial_x \phi(X_1, Y_1) + \Delta Y \partial_y \phi(X_1, Y_1)$$

We define $k_x = \partial_x \phi(X_1, Y_1)$ and $k_y = \partial_y \phi(X_1, Y_1)$ and

$$\mathbb{E}[\frac{\Delta X \Delta Y}{|\Delta Z|}] = \mathbb{E}[\frac{\Delta X \Delta Y}{|k_x \Delta X + k_y \Delta Y|}]$$

As long as $k_x > 0$ and $k_y > 0$ (which can be assured simply by defining X and Y appropriately), the proof of Proposition 7 is not changed. Thus the relation

$$\int_0^\infty \sigma_{XY}(t)dt = \mathbb{E}[\frac{\Delta X \Delta Y}{|\Delta Z|}] \leq 0$$

holds primarily because of the additive component of whatever ϕ may be.

COROLLARY 2. *Assume that the distribution of (X_i, Y_i) has finite support, i.e. there is $K > 0$ such that $\mathbb{P}(X_i \in [-K, K], Y_i \in [-K, K]) = 1$ and that $|\kappa| < (a \wedge b)/K$, where $a \wedge b$ denotes the minimum between a and b. If we have*

$$\mathbb{E}\left[\frac{|\Delta X \Delta Y|}{|Z(\kappa)|}\right] = \infty, \tag{34}$$

then

$$\mathbb{E}\left[\frac{\Delta X \Delta Y}{|Z(\kappa)|}\right] = -\infty.$$

Proof: Note first that, if $|\kappa| < (a \wedge b)/K$, then $\mathbb{P}(\, a + \kappa Y_1 \geq a - |\kappa K|,\, b + \kappa X_2 \geq b - |\kappa K|) = 1$, and hence

$$\begin{aligned}
\mathbb{E}\left[\frac{\Delta X \Delta Y \mathbb{1}_{\Delta X \Delta Y > 0}}{|Z(\kappa)|}\right] &= E\left[\frac{\Delta X \Delta Y \mathbb{1}_{\Delta X \Delta Y > 0}}{|(a+\kappa Y_1)\Delta X + (b+\kappa X_2)\Delta Y|}\right] \\
&= E\left[\frac{\Delta X \Delta Y \mathbb{1}_{\Delta X \Delta Y > 0}}{|(a+\kappa Y_1)\Delta X| + |(b+\kappa X_2)\Delta Y|}\right] \\
&\leq \frac{2}{(a \wedge b) - |\kappa K|} E\left[\frac{|\Delta X \Delta Y|}{|\Delta X| + |\Delta Y|}\right] \\
&\leq \frac{1}{(a \wedge b) - |\kappa K|} E\left[\sqrt{|\Delta X \Delta Y|}\right] \leq \frac{K}{a \wedge b} < \infty.
\end{aligned}$$

Therefore, condition (34) implies that

$$\mathbb{E}\left[\frac{|\Delta X \Delta Y| \mathbb{1}_{\Delta X \Delta Y < 0}}{|Z(\kappa)|}\right] = \infty,$$

and thus,

$$\mathbb{E}\left[\frac{\Delta X \Delta Y}{|Z(\kappa)|}\right] = \mathbb{E}\left[\frac{\Delta X \Delta Y \mathbb{1}_{\Delta X \Delta Y > 0}}{|Z(\kappa)|}\right] - \mathbb{E}\left[\frac{|\Delta X \Delta Y| \mathbb{1}_{\Delta X \Delta Y < 0}}{|Z(\kappa)|}\right] = -\infty,$$

achieving the proof. □

Alternative proof 1

Let $f(x, y)$ denote the probability density governing random variables ΔX and ΔY. The only restrictions we place on $f(x, y)$ is that it be symmetric about zero in both x and y directions and that its tails be not too heavy so that the following integral exists in each quadrant of the x-y plane. Both of these restrictions seem quite reasonable from a biological standpoint. The expectation may be thus be written as follows:

$$\mathbb{E}[\frac{\Delta X \Delta Y}{|\Delta Z|}] \;=\; \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \frac{xy}{|x+y|} f(x,y) dx dy$$

Symmetry about zero ($f(x, y) = f(-x, y)$ and $f(x, y) = f(x, -y)$) allows us to integrate quadrant-by-quadrant as follows:

$$\begin{aligned}
\mathbb{E}[\frac{\Delta X \Delta Y}{|\Delta Z|}] \;&=\; \int_0^{\infty} \int_0^{\infty} \left(\frac{xy}{|x+y|} + \frac{(-x)y}{|(-x)+y|} + \frac{(-x)(-y)}{|(-x)+(-y)|} + \frac{x(-y)}{|x+(-y)|} \right) f(x,y) dx dy \\
&=\; \int_0^{\infty} \int_0^{\infty} \left(\frac{2xy}{x+y} - \frac{2xy}{|x-y|} \right) f(x,y) dx dy \\
&=\; \int_0^{\infty} \int_0^{\infty} \left(\frac{1}{x+y} - \frac{1}{|x-y|} \right) 2xy f(x,y) dx dy \qquad (35)
\end{aligned}$$

We are now integrating over positive values of x and y, for which:

$$(x+y)^2 = x^2 + 2xy + y^2 \geq x^2 - 2xy + y^2 = (x-y)^2$$
$$\sqrt{(x+y)^2} \geq \sqrt{(x-y)^2}$$
$$x + y \geq |x-y|$$

so that:

$$\frac{1}{x+y} - \frac{1}{|x-y|} \leq 0$$

implying that Eq (35) is non-positive, hence giving the result:

$$\int_0^\infty \sigma_{XY}(t)dt \leq 0$$

Alternative proof 3.

Define: $X = u|X|$ and $Y = v|Y|$, where u, v are independent $+/-1$ random variables, independent of $|X|$ and $|Y|$. Then: $|u|X| + v|Y|| = w(|X| + |Y|) + (1-w)||X| - |Y||$, where $w = uv$. Again, w is independent of $|X|$ and $|Y|$.

And:

$$\begin{aligned}\mathbb{E}[XY/|X+Y|)] &= \mathbb{E}[w|X||Y|/(w(|X|+|Y|) + (1-w)||X|-|Y||)] \\ &= \frac{1}{2}\mathbb{E}[|X||Y|/((|X|+|Y|)] - \frac{1}{2}\mathbb{E}[|X||Y|/||X|-|Y||] \\ &< 0\end{aligned}$$

since $|X| + |Y| \geq ||X| - |Y||$. □

Addendum to alternative proof 3: Prop 7 holds generally for divergent expectations.

Remark: The proof of this addendum extends and succinctly generalizes the proof of Corollary 2.

Proof:

Set $U = |X|$ and $V = |Y|$; $M = \text{Max}(U, V)$, $m = \text{Min}(U, V)$. Then you can rewrite the expectation as:

$$\begin{aligned} E[UV\{1/(U+V) - 1/(|U-V|)\}] &= E[mM\{-2m/(M^2 - m^2)\}] \\ &= -2E[Mm^2/(M^2 - m^2)] \leq 0 \end{aligned}$$

Indeed, if the expectation is infinity, we get a -infinity as our answer. This approach removes the need to make the argument that $U + V > |U - V|$ and avoids the need to take a difference of expectations. □

Metapopulation simulations illustrate how both *products* and *process* of natural section promote recombination

Our mathematical analyses of across- and within-population covariance by themselves reveal something fundamental about evolution: selection pressure for recombination is an unavoidable consequence of natural selection. These results, however, derive from somewhat non-traditional approaches and abstract math. To put our findings in perhaps a more familiar and tangible setting, we simulated the evolution of a structured metapopulation (with no migration). To avoid introducing the complexities of mutation, which will be addressed in a subsequent study, we here simply add uncorrelated gaussian noise to X and Y every one hundred generations so that the population undergoes repeated bouts of selection. Extended Data Fig. 11 plots covariance and correlation dynamics from these simulations. The theory we have developed here (and in the SI for the case of many alleles) makes quantitative and qualitative predictions about the change in both across- and within-deme covariance over the course of each bout of selection. As our theory predicts, 1) within-deme covariance immediately plunges below zero despite starting out very strongly positive; put differently, the *process* of natural selection favours recombination, and 2) across-deme covariance is reduced in the first bout of selection but does not immediately go below zero; it is not until the third bout of selection that it dips below zero; put differently, the *products* of natural selection favour recombination. (We note that within-deme *correlation* does not go below zero in the first bout of selection, but this is due to an averaging problem introduced by indeterminate correlations when covariance is near zero.)

Modifier evolution under selection and no mutation

Pertaining to:

- Extended Data Fig. 4
- Extended Data Fig. 5

- Extended Data Fig. 6
- Extended Data Fig. 7

Notation:

- D denotes "donor"
- R denotes "recipient"
- superscript + indicates that the individual must be recombination competent (rec^+)
- no superscript indicates that the individual can be either rec^+ or rec^-.
- one-way arrow indicates one-way gene transfer where the donor's gene is duplicated and the recipient acquires the duplicate copy.
- two-way arrow indicates a two-way gene transfer, or a gene swap between the two individuals.
- Example: $D \to R^+$ indicates a one-way gene transfer from donor to recipient, where the donor can have either *rec* status but the recipient must be rec^+.

References

[1] R. Bürger. Moments, cumulants, and polygenic dynamics. *J. Math. Biol.*, 30(2):199–213, 1991.

[2] R. Bürger. Mathematical properties of mutation-selection models. *Genetica*, 102:279, 1998.

[3] W. J. Ewens. *Mathematical Population Genetics: I. Theoretical Introduction*. Springer, New York, NY, 2004.

[4] P. J. Gerrish, A. Colato, and P. D. Sniegowski. Genomic mutation rates that neutralize adaptive evolution and natural selection. *J. R. Soc. Interface*, 10(85):20130329, Aug. 2013.

[5] P. J. Gerrish and P. D. Sniegowski. Real time forecasting of near-future evolution. *J. R. Soc. Interface*, 9(74):2268–2278, Sept. 2012.

[6] M.-E. Gil, F. Hamel, G. Martin, and L. Roques. Mathematical properties of a class of integro-differential models from population genetics. *SIAM J. Appl. Math.*, 77(4):1536–1561, Jan. 2017.

[7] K. Joag-Dev and F. Proschan. Negative association of random variables with applications. *Ann. Statist.*, 11(1):286–295, 1983.

[8] G. Martin and L. Roques. The nonstationary dynamics of fitness distributions: Asexual model with epistasis and standing variation. *Genetics*, 204(4):1541–1558, Dec. 2016.

Natural selection and the advantage of recombination

Extended Data

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Extended Data Table 1 | Notation for m-locus case

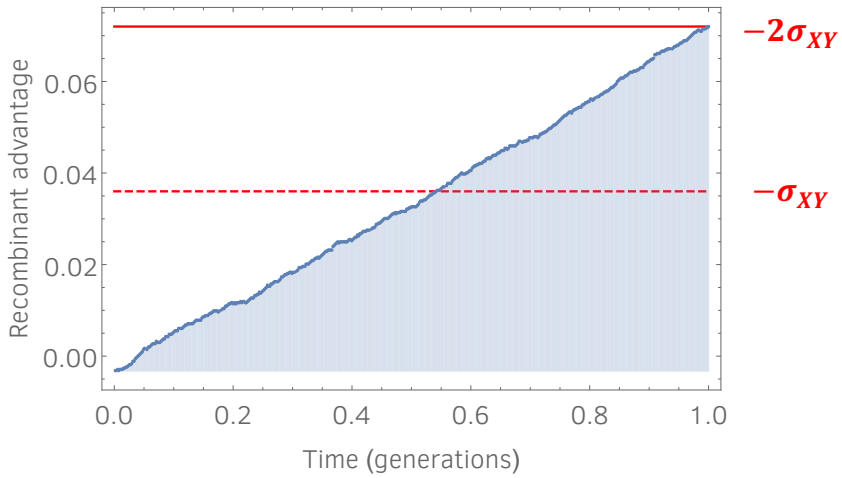
$X_{i,j}$	random variable quantifying a fitness-related phenotype encoded by the j^{th} allele of the i^{th} genotype
Z_i	organismal fitness of the i^{th} genotype
ϕ	fitness function: $Z_i = \phi(X_{i,1}, X_{i,2}, X_{i,3}, ..., X_{i,m})$
$Z^{[k]}$	k^{th}-ranked genotype, ranked by fitness; $k = 1$ lowest fitness, $k = n$ highest fitness, to square with order-statistic notation (standard notation: $Z^{[k:n]}$)
$X_{(k),j}$	j^{th} fitness-related phenotype (j^{th} locus) of the k^{th}-ranked genotype (j^{th} *concommitant* of order statistic $Z^{[k]}$)

Extended Data Table 2 | Notation for 2-locus case

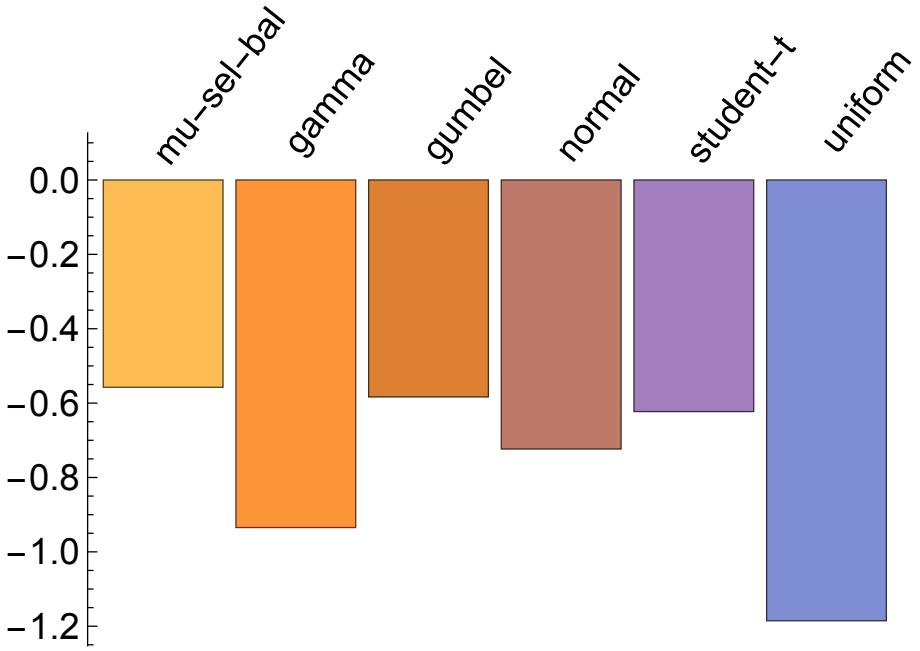
X, Y	random variables quantifying two fitness-related phenotypes encoded by two loci
Z	organismal fitness
ϕ	fitness function: $Z = \phi(X, Y)$
X_k, Y_k	random variables quantifying two fitness-related phenotypes encoded by two loci in the k^{th} genotype
Z_k	organismal fitness of k^{th} genotype
$Z^{[k]}$	k^{th}-ranked genotype, ranked by fitness; $k = 1$ lowest fitness, $k = n$ highest fitness, to square with order-statistic notation (standard notation: $Z^{[k:n]}$)
$X_{(k)}$, $Y_{(k)}$	quantified phenotypes contributing to the fitness of the k^{th}-ranked genotype (*concommitants* of order statistic $Z^{[k]}$)
$\mathtt{Cov}(X, Y) = \sigma_{XY}$	covariance between fitness-related phenotypes X and Y
σ_X^2, σ_Y^2	variance in X and Y, respectively
$\kappa_{i,j}$	$(i, j)^{th}$ cumulant in (X, Y)
$u(x, y, t)$	probability density in fitness-related phenotypes x and y at time t: $\int_{x,y} u(x, y, t) = 1$
$\Phi(\varphi, \theta, t) = \Phi_t(\varphi, \theta)$	characteristic function of density $u(x, y, t)$ at time t
$\Phi(\varphi, \theta) = \Phi_0(\varphi, \theta)$	characteristic function of density $u(x, y, t)$ at time $t = 0$
$\mathcal{C}(\varphi, \theta, t) = \mathcal{C}_t(\varphi, \theta)$	log of the characteristic function (cumulant-generating function) of density $u(x, y, t)$ at time t
$\mathcal{C}(\varphi, \theta) = \mathcal{C}_0(\varphi, \theta)$	log of the characteristic function (cumulant-generating function) of density $u(x, y, t)$ at time $t = 0$
$g(x, y, t)$	probability density of mutational effects in x and y (the DFE) at time t
$g(x, y)$	time-invariant probability density of mutational effects in x and y (time-invariant DFE)
$\mathcal{M}(\varphi, \theta, t)$	characteristic function of density $g(x, y, t)$ (the DFE) at time t
$\mathcal{M}(\varphi, \theta)$	characteristic function of the time-invariant density $g(x, y)$ (time-invaraint DFE)

Extended Data Table 3 | Notation continued

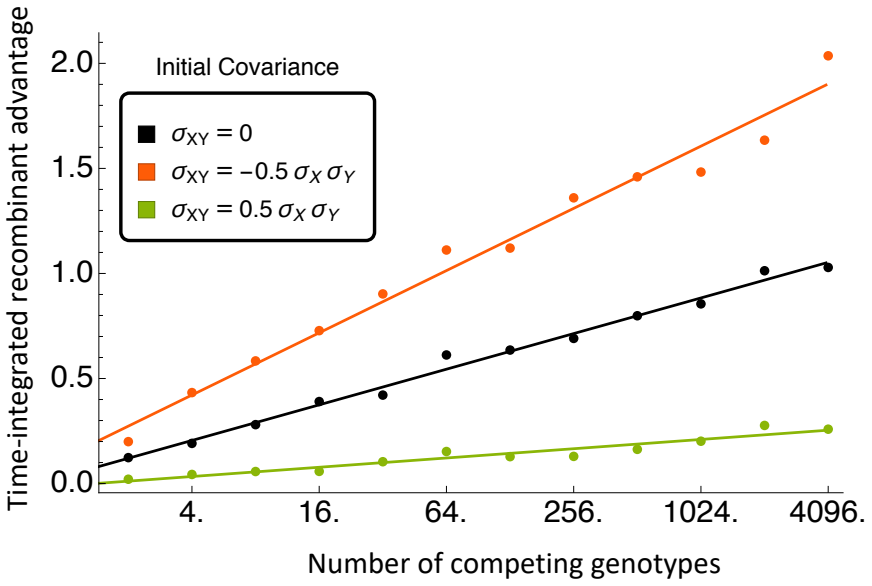
$\bullet^{(i,j)}$	i^{th} and j^{th} partial derivatives with respect to the first and second arguments of $\bullet$, respectively
$\partial_\bullet$	partial derivative with respect to $\bullet$
U	genomic mutation rate
n	number of distinct genotypes in a population
N	population size
$m_{i,j}$	$(i,j)^{th}$ raw (non-centralized) moment of the DFE
$\tilde{\Phi}(\varphi,\theta,t) = \tilde{\Phi}_t(\varphi,\theta)$	empirical characteristic function of fitness density at time t
$\tilde{\Phi}(\varphi,\theta) = \tilde{\Phi}_0(\varphi,\theta)$	empirical characteristic function of fitness density at time $t = 0$
$\tilde{\mathcal{C}}(\varphi,\theta,t) = \tilde{\mathcal{C}}_t(\varphi,\theta)$	log of the empirical characteristic function (empirical cumulant-generating function) of fitness density at time t
$\tilde{\mathcal{C}}(\varphi,\theta) = \tilde{\mathcal{C}}_0(\varphi,\theta)$	log of the empirical characteristic function (empirical cumulant-generating function) of fitness density at time $t = 0$
$\bar{s}_X = -m_{1,0}$	mean deleterious effect of mutation on phenotype x.
$\bar{s}_Y = -m_{0,1}$	mean deleterious effect of mutation on phenotype y.
$\bar{x}(t) = \mathbb{E}[X(t)]$	mean X at time t
$\bar{y}(t) = \mathbb{E}[Y(t)]$	mean Y at time t
$\bar{w}_r(t)$	predicted mean recombinant fitness at time t
$\bar{s}_r(t)$	predicted mean recombinant selective advantage at time t
$\mathbb{1}_A$	indicator function: 1 when condition A is met, 0 otherwise.



Extended Data Fig 1 | Dynamics of recombinant advantage over one generation. A population of size $N = 500$ was simulated using a Moran model of evolution. Every individual in the population has unique values for X and Y: specifically, the i^{th} individual has genic fitnesses X_i and Y_i. The X_i and Y_i values are drawn at random from a bivariate distribution with negative covariance σ_{XY}. Ten recombinants are introduced at time zero, and their fitness advantage is recorded over the course of one generation. As predicted, recombinant advantage increases to $-2\sigma_{XY}$ over the course of one generation. This increase is observed here to be linear, from which we surmise that *mean* recombinant advantage over this single generation is $-\sigma_{XY}$.

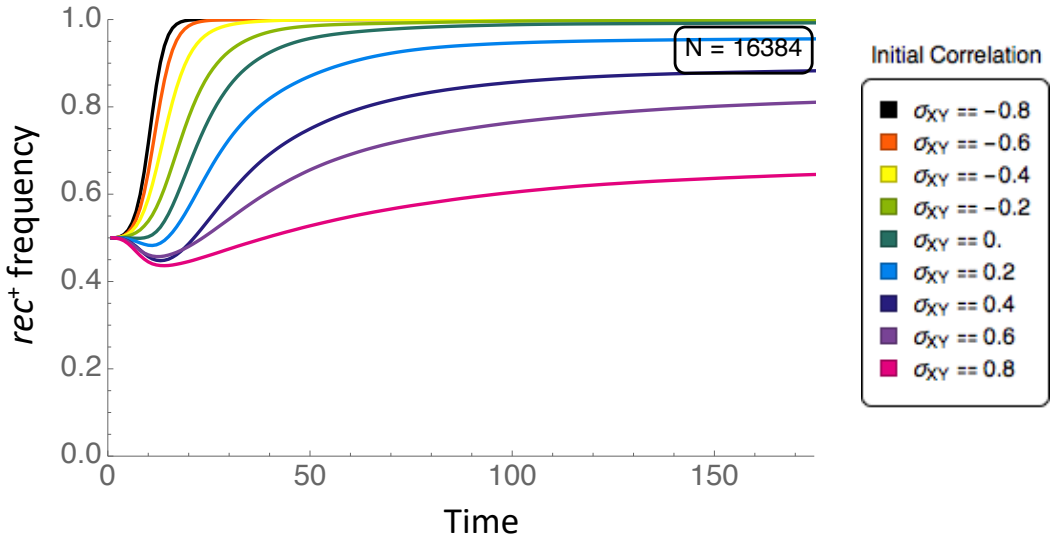


Extended Data Fig 2 | Time-integrated covariance as a function of distribution. Time-integrated covariance as predicted by Eq (31). Values plotted were computed by Montecarlo integration, where X and Y are drawn from a bivariate distribution indicated above each bar. For all distributions, $\mathbb{E}[X] = \mathbb{E}[Y] = -0.1$, and $\mathbb{V}[X] = \mathbb{V}[Y] = 0.04$, and correlation coefficient was drawn at random from a uniform distribution over the interval $(-1, 1)$. Montecarlo integration sample size was $10,000$. With the exception of the normal distribution, all bivariate distributions were computed as copula of two univariate distributions.

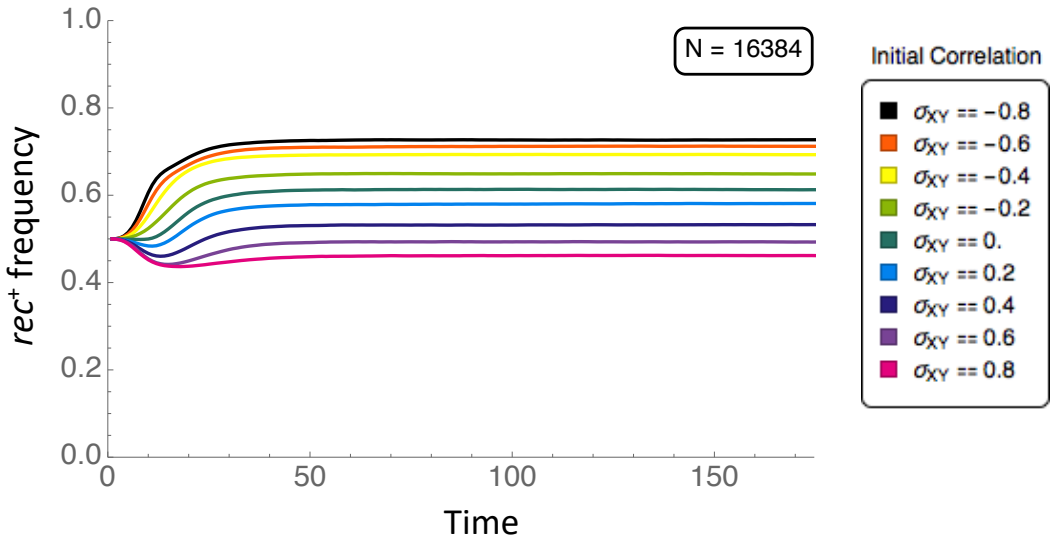


Extended Data Fig 3 | Time-integrated recombinant advantage increases with number of genotypes. Time-integrated recombinant advantage computed as minus one times the time-integrated covariance as predicted by Eq (31). Values plotted were computed by Montecarlo integration, where X and Y were drawn from a bivariate normal distribution with $\mathbb{E}[X] = \mathbb{E}[Y] = -0.1$, and $\mathbb{V}[X] = \mathbb{V}[Y] = 0.04$, and initial covariance is indicated by color. Montecarlo integration sample size was $10,000$ for each point.

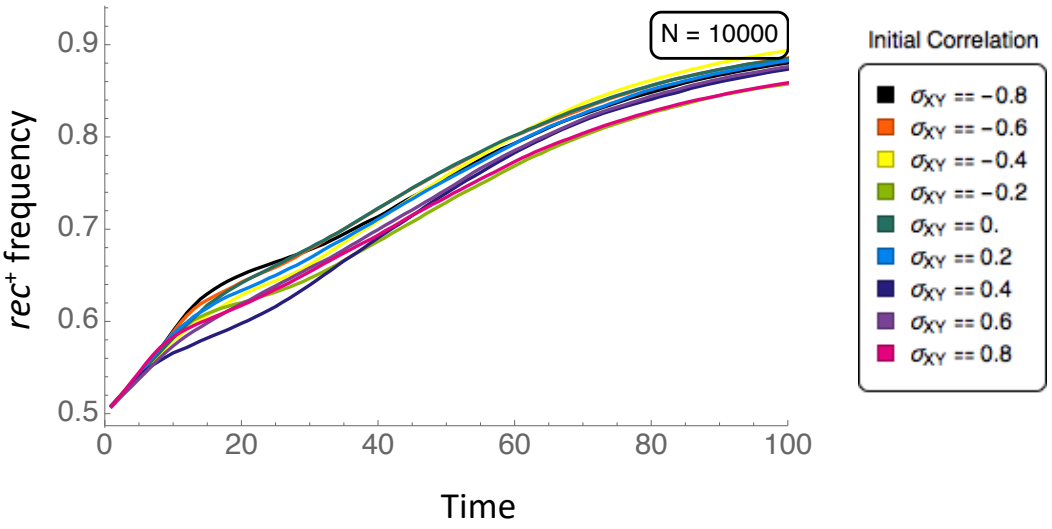
Extended Data Fig 4 | Three-locus model. To assess the effect of natural selection on a recombination modifier under our simple setting with no mutation, we employ a 3-locus model, two of which are fitness loci (X and Y), and the third of which is a recombination modifier. The recombination modifier has two states: rec^+ or rec^-. A population of n pairs of X and Y fitnesses are drawn at random from a bivariate normal distribution with correlation indicated by color. Half of those pairs of fitnesses are linked to a rec^+ allele and the other half are linked to a rec^- allele. Natural selection acts on this variation until all fitness variation is purged. Plotted is the average rec^+ frequency of 100 simulated populations for each initial correlation.



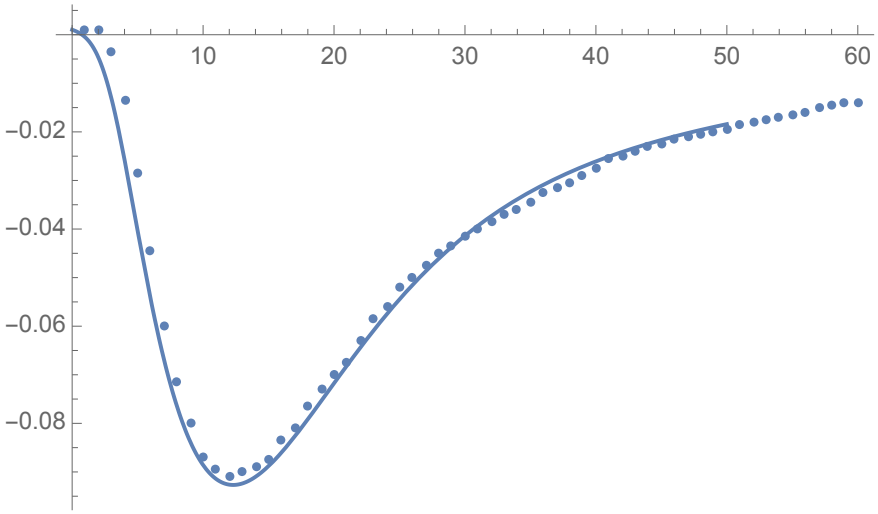
Extended Data Fig 5 | Reciprocal gene swap (two-way gene transfer) between two rec-competent individuals. A population of n pairs of X and Y fitnesses are drawn at random from a bivariate normal distribution with correlation indicated by color. Half of those pairs of fitnesses are linked to a rec^+ allele and the other half are linked to a rec^- allele. Natural selection acts on this variation until all fitness variation is purged. Plotted is the average rec^+ frequency of 100 simulated populations for each initial correlation. To form a recombinant, two rec^+ individuals are chosen at random. One of the three genes is chosen at random and this gene is swapped between the two individuals: $R^+ \leftrightarrow D^+$.



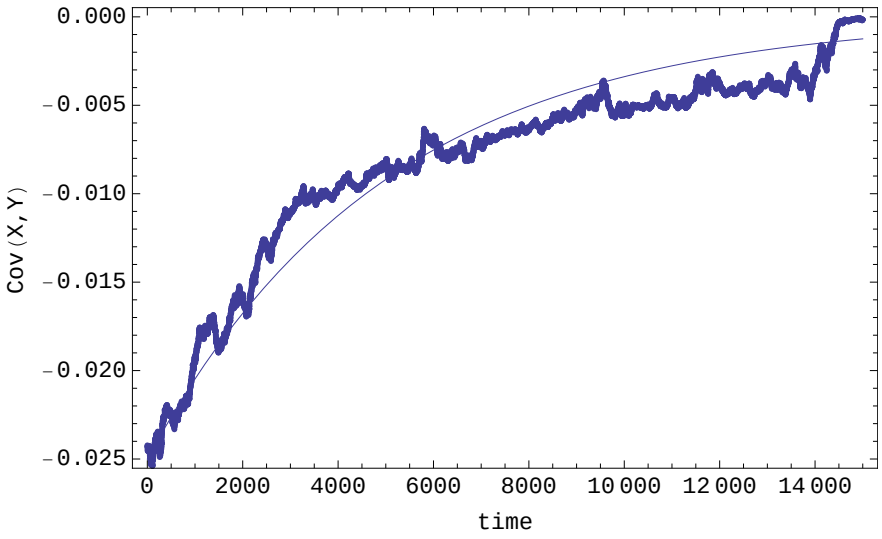
Extended Data Fig 6 | Rec-competent recipient, donor chosen at random (two-way gene transfer). A population of n pairs of X and Y fitnesses are drawn at random from a bivariate normal distribution with correlation indicated by color. Half of those pairs of fitnesses are linked to a rec^+ allele and the other half are linked to a rec^- allele. Natural selection acts on this variation until all fitness variation is purged. Plotted is the average rec^+ frequency of 100 simulated populations for each initial correlation. To form a recombinant, one rec^+ individual is chosen at random to be the recipient (R), and a second individual is chosen at random regardless of its *rec* status to be the donor (D). One of the three genes is chosen at random and this gene is swapped between the two individuals: $R^+ \leftrightarrow D$.



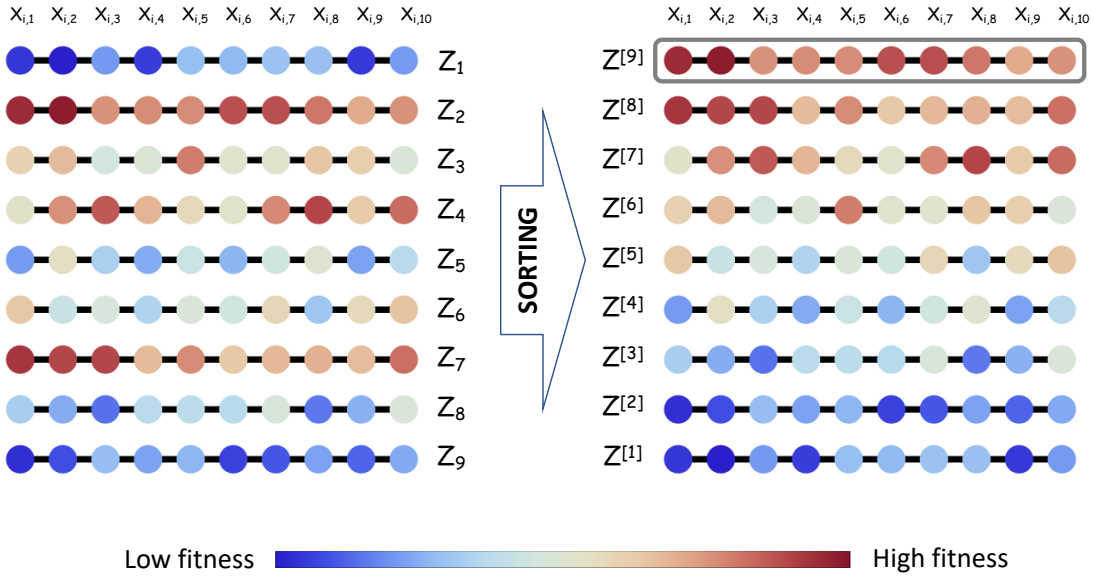
Extended Data Fig 7 | Rec-competent donor, recipient chosen at random (one-way gene transfer), Poisson number of genes transferred. A population of n pairs of X and Y fitnesses are drawn at random from a bivariate normal distribution with correlation indicated by color. Half of those pairs of fitnesses are linked to a rec^+ allele and the other half are linked to a rec^- allele. Natural selection acts on this variation until all fitness variation is purged. Plotted is the average rec^+ frequency of 100 simulated populations for each initial correlation. To form a recombinant, one rec^+ individual is chosen at random to be the donor (D), and a second individual is chosen at random regardless of its *rec* status to be the recipient (R). A truncated Poisson number of genes with mean 0.1 is chosen at random, and the recipient acquires this gene set from the donor (one-way transfer): $D^+ \rightarrow R$.



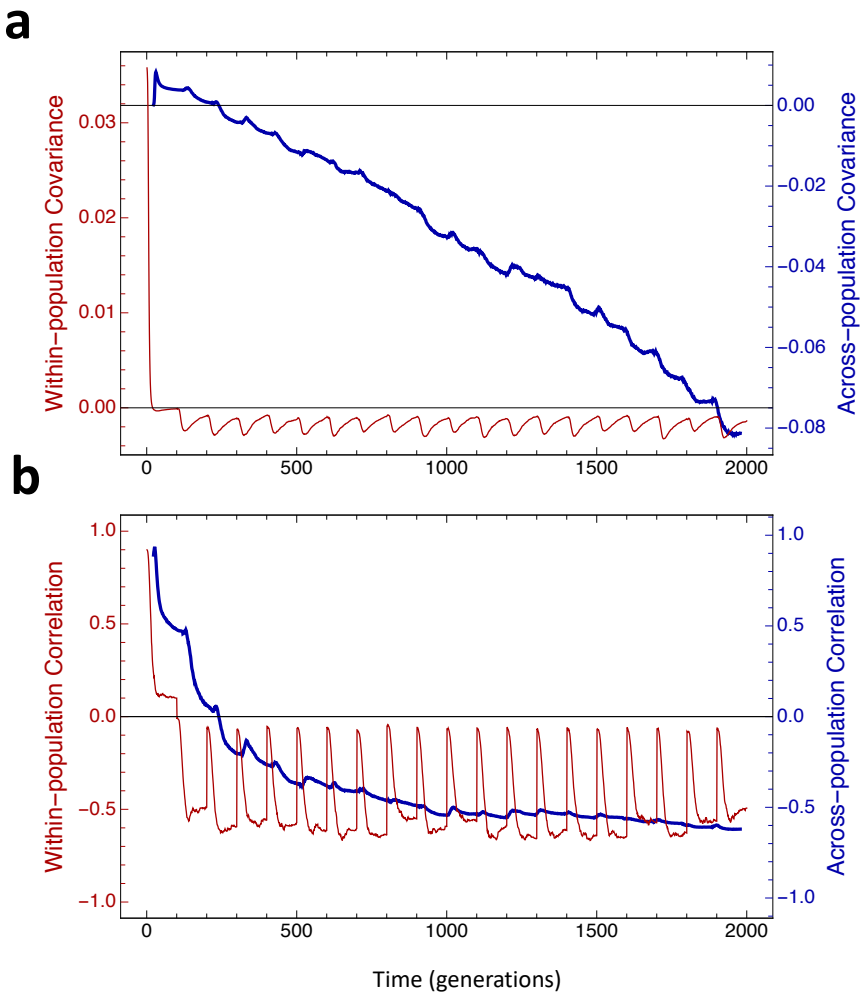
Extended Data Fig 8 | Forecasting covariance evolution. Horizontal axis is time (generations). Vertical axis is covariance. Points are covariances measure from a completely stochastic, individual-based, simulation. Solid curve is the covariance predicted by empirical cumulant-generating function at time zero (the initial condition to the simulation), denoted $\tilde{\mathcal{C}}(\varphi, \theta)$ and defined in the main text.



Extended Data Fig 9 | Covariance dynamics under drift only. Solid curve plots the predicted dynamics given by Eq (9) and assuming $n = N$; points plot the averages of 50 simulations. The initial state of the population was a set of 5000 (X, Y) pairs ($N = 5000$) drawn at random from a bivariate normal distribution with $\sigma_{XY}(0) = -0.025$.



Extended Data Fig 10 | General formulation. The population here consists of $n = 9$ individuals (9 genomes) represented by the 9 rows, each of which carries a genome with $m = 10$ loci represented by the 10 columns. Each dot represents a locus on an individual genome and its color indicates its genic fitness. The total fitness of the i^{th} individual is $Z_i = \phi(X_{i,1}, X_{i,2}, ..., X_{i,m})$, where $X_{i,j}$ is the genic fitness of j^{th} locus in the i^{th} individual. Strictly speaking, ϕ can be any function, but our developments eventually require that it be some increasing function of the genic fitnesses, $X_{i,j}$. To give a simple and useful example, ϕ may be defined simply as the sum of its arguments. We employ this definition of ϕ extensively in the main text and in our analyses, both because of its simplicity and because of its connection to classical population genetics and notions of additive fitness. On the left-hand side, the genomes are not sorted in any order; on the right-hand side, the same genomes are sorted (ranked) by their total fitness, Z, such that $Z^{[1]}$ is the genome of lowest fitness and $Z^{[n]}$ is the genome of highest fitness. If selection were deterministic, the fittest genome ($Z^{[n]}$, highlighted by a frame) would eventually displace all other genomes. The statistical properties of the genic fitnesses of this fittest genome are thus of special interest from an evolutionary perspective. In particular, we are here interested in any statistical associations among these genic fitnesses: if that association tends to be negative, then recombination will be favored.



Extended Data Fig 11 | Covariance dynamics in a metapopulation. Simulated metapopulations of size $N = 500$ begin with all individuals being assigned unique genic fitness pairs, (X, Y), drawn at random from a common bivariate normal distribution with correlation coefficient 0.9, means -0.1 and variances 0.2. Every 100 generations, uncorrelated gaussian noise was injected as follows: $X' = X + Q$ and $Y' = Y + Q$, where $Q \sim \mathcal{N}(-.1, .1)$. Plotted is mean covariance (**a**) and mean correlation (**b**) of 2000 runs.