SUPPLEMENTAL MATERIAL: EVOLUTION IN ALTERNATING ENVIRONMENTS WITH TUNABLE INTER-LANDSCAPE CORRELATIONS

The Supplemental Material contains semi-analytic approximations for the number of local maxima in a single landscape and the probability of shared maxima in paired landscapes. It also includes seven supplemental figures (S1-S7).

Semi-analytical approximations to describe local maxima

Dynamics in alternating environments are often impacted by the presence of shared local maxima. Here we derive semi-analytical approximate expressions for several key quantities. While exact expressions are difficult to obtain, even for the simple model used here, we derive below several approximations that involve cumulative distribution functions (CDFs) for common distributions (e.g. multivariate normal) and/or Gaussian-like integrals that can be easily calculated numerically.

Number of local maxima in a single landscape

Rugged landscapes ($\sigma > 0$) potentially have multiple local maxima. To approximate the expected number of local maxima, consider a landscape with N loci so that each genotype has a total of N nearest neighbor genotypes. In a purely additive ($\sigma = 0$) landscape, a mutation in gene i changes the fitness by an amount ϵ_i drawn from a uniform distribution [0,1]. In a rugged landscape, the fitness of each genotype also contains an additive contribution from epistasis–in this case, a zero-mean, normally distributed random variable with variance σ^2. The fitness of each genotype is therefore a sum of (up to N) uniform variables and a single normally distributed variable.

To estimate the expected number of maxima in a landscape, consider a particular genotype with a fixed fitness $f = f_\epsilon + f_\sigma$, where f_ϵ is the total fitness contribution from any mutations and f_σ is the contribution from epistasis. The genotype will have N neighbors, each differing by a single mutation; the fitness of neighbor i has a fitness of the form $f_i = f_\epsilon + \epsilon_i + \sigma_i$, where ϵ_i is a uniform random variable accounting for adding or subtracting one mutation, and σ_i is a normal random variable accounting for epistasis. The f_ϵ term is a fixed value–the same as for the focal genotype. In a statistical ensemble of such neighbors, the probability that $f > f_i$, that is, the probability that the genotype in question has a higher fitness than one particular neighbor is given by

$$p^i_{max}(f_\sigma) = \int_{-\infty}^{f_\sigma} dx\, p_+(x), \tag{S1}$$

where $p_+(x)$ is the probability density function (pdf) for the sum $\sigma_i + \epsilon_i$. Since the pdf for a sum of random variables is given by the convolution of their individual pdfs, we have

$$p^i_{max}(f_\sigma) = \frac{1}{2}\int_{-\infty}^{f_\sigma} dx \int_{-1}^{1} du\, \phi_{\sigma_i}(x-u), \tag{S2}$$

where $\phi_\sigma(x)$ is the pdf of a zero-mean normal variable with variance σ^2,

$$\phi_\sigma(x) \equiv \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{x^2}{2\sigma^2}\right). \tag{S3}$$

Equation S2 can also be written as

$$p^i_{max}(f_\sigma) = \frac{1}{2}\int_{-1}^{1} du\, F_{\sigma_i}(f_\sigma + u), \tag{S4}$$

where $F_{\sigma_i}(x)$ is the cumulative distribution function for the variable σ_i (and in this case, each σ_i is a zero-mean normal variable with variance σ^2). The integral above can be written as a linear sum of error functions, though it is somewhat cumbersome and we do not write it out here.

The probability that the genotype in question is a local max–that is, has a fitness larger than each of its N nearest neighbors–is approximately

$$p_{max}(f_\sigma) \approx \left(p^i_{max}(f_\sigma)\right)^N \tag{S5}$$

where we have assumed that each neighbor can be treated as independent from the others. The average probability that a genotype is a local maximum is then given by integrating over the distribution for f_σ,

$$P_{max} = \int_{-\infty}^{\infty} df_\sigma\, \phi_\sigma(f_\sigma)\, p_{max}(f_\sigma) = \langle p_{max}(x) \rangle \tag{S6}$$

where brackets $\langle\cdot\rangle$ represent an average over a normal distribution with variance σ^2. If we assume that the 2^N different genotypes in a landscape are approximately independent, the expected number of maxima is then given by

$$N_{max} = 2^N P_{max}. \tag{S7}$$

Equation S7 is difficult to evaluate analytically but easy to solve numerically, and the approximation closely matches results from randomly generated landscapes (Figure 3). For small epistasis ($\sigma \ll 1$), we can expand $p_{max}(f_\sigma)$ about the average $\langle f_\sigma\rangle$ to arrive at the approximation

$$N_{max} \approx 1 + \frac{1}{2}N(N-1)\sigma^2. \tag{S8}$$

Similarly, for large epistasis ($\sigma \to \infty$), we have $P_{max} \approx (N+1)^{-1}$; intuitively, all genotypes in a local neighborhood (the focal genotype and its N nearest neighbors) are equally likely to be the maximum, and the expected number of maxima therefore approaches $N_{max} = 2^N/(N+1)$.

Shared maxima between correlated landscapes

Given that a particular genotype corresponds to a local maximum in landscape A, we would like to estimate the probability that it is also a maximum in the paired landscape B. To do so, consider a genotype that is a local maximum in landscape A. Let the fitness of that genotype be a_1 and the fitness of its N nearest neighbors be $a_2 > a_3 ... > a_{N+1}$, where we have labeled the neighbors according to their ranked fitness. We would like to calculate the conditional probability $p(b_1, b_2..b_{N+1}|a_1, a_2..a_{N+1})$ that describes the fitness values $\{b_i\}$ of the corresponding genotypes in landscape B, which is correlated with landscape A with correlation ρ.

In the limit of large epistasis ($\sigma \to \infty$), the fitness variables $\{a_i\}$ and $\{b_i\}$ are jointly distributed normal variables with mean $\bar{\mu} = (\mu_{a_1}, \mu_{a_2}, \ldots, \mu_{a_{N+1}}, \mu_{b_1}, \mu_{b_2} \ldots \mu_{b_{N+1}}) = (0, 0, \ldots, 0)$ and covariance matrix

$$\Sigma = \begin{pmatrix} \Sigma_{aa} & \Sigma_{ab} \\ \Sigma_{ab} & \Sigma_{bb} \end{pmatrix} \tag{S9}$$

made of $(N+1) \times (N+1)$ sub-matrices

$$\Sigma_{aa} = \Sigma_{bb} = \sigma^2 \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix} \tag{S10}$$

and

$$\Sigma_{ab} = \sigma^2 \begin{pmatrix} \rho & 0 & \dots & 0 \\ 0 & \rho & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \rho \end{pmatrix} \tag{S11}$$

The matrix Σ_{aa} (Σ_{bb}) describes the covariance relationships between the focal genotype in landscape A (B) and each of its N nearest neighbors. The matrix Σ_{ab} describes the covariance between fitness values for the local neighborhood of $N+1$ genotypes in landscapes A and B. If we treat the fitness values $\{a_i\}$ as fixed and the fitness values $\{b_i\}$ as random variables, the conditional probability $p(b_1, b_2, \dots b_{N+1} | a_1, a_2, \dots a_{N+1})$ is also normally distributed, with mean vector $\bar{\mu}_{cond} = \rho(a_1, a_2, \dots, a_{N+1})$ and covariance

$$\Sigma_{cond} = \sigma^2 \begin{pmatrix} 1-\rho^2 & 0 & \dots & 0 \\ 0 & 1-\rho^2 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1-\rho^2 \end{pmatrix} \tag{S12}$$

We would like to know the probability of b_1 corresponding to a local maximum in landscape B given that a_1 corresponds to a local maximum in landscape A. To do so, we consider the N variables $\delta_i \equiv b_i - b_{i-1}$, whose distribution (conditioned on a specific set of values $\{a_i\}$) is a multivariate normal with mean $\bar{\mu}_\delta = \rho(a_1 - a_2, a_1 - a_2, \dots, a_1 - a_{N+1})$ and covariance

$$\Sigma_\delta = \sigma^2 \begin{pmatrix} 2-2\rho^2 & 1-\rho^2 & \dots & 1-\rho^2 \\ 1-\rho^2 & 2-2\rho^2 & \dots & 1-\rho^2 \\ \vdots & \vdots & \ddots & \vdots \\ 1-\rho^2 & 1-\rho^2 & \dots & 2-2\rho^2 \end{pmatrix} \tag{S13}$$

Hence, if we are given a specific set of fitness values $\{a_i\}$, with a_1 the maximum of the local fitness neighborhood in landscape A, the probability that the fitness is also a maximum in the B landscape is given by

$$p_{\text{shared}}(\sigma, \rho) = 1 - \bar{F}_{\delta,\bar{a}}(\bar{0}) \tag{S14}$$

where $\bar{F}_{\delta,\bar{a}}(\bar{x})$ is the cumulative distribution function (CDF) for the multivariate normal with mean $\bar{\mu}_\delta$ and covariance Σ_δ (conditioned on a set of values $\bar{a} = (a_1, a_2, \ldots, a_{N+1})$) and $\bar{0}$ is the zero vector. Specifically, we have

$$\bar{F}_{\delta,\bar{a}}(\bar{x}) = \int_{-\infty}^{x_1} dz_1 \int_{-\infty}^{x_2} dz_2 \ldots \int_{-\infty}^{x_N} dz_N \, \frac{1}{(2\pi)^{N/2}|\Sigma_\delta|^{1/2}} \exp\left((\bar{z} - \bar{\mu}_\delta)^T \Sigma_\delta^{-1} (\bar{z} - \bar{\mu}_\delta)\right) \tag{S15}$$

where x_i is component i of $\bar{x}$. While there is no closed expression for the CDF of a multivariate Gaussian, there are many algorithms to rapidly calculate it numerically, and many scientific computing platforms even have built-in functions for this purpose.

To complete our approximation, we must choose specific values of the fixed variables $\{a_i\}$ on which the approximation is conditioned. In what follows, we consider two choices that lead to approximate expressions in the limits of of large and small epistasis.

In the limit of large epistasis, the fitness values in the local neighborhood $\{a_i\}$ are uncorrelated, Gaussian variables with variance σ^2. We therefore choose a_i to be the expected value of the i-th largest value in a sample of Gaussian variables (i.e. an order statistic (David and Nagaraja 2004)); without loss of generality, we assume the variables have mean zero. While there is no analytical expression for the expected value of the order statistics for normal variables, multiple approximations have been proposed. Here, we use the approximation in Royston (1982), which gives for our $N + 1$ fitness variables

$$a_i \approx \Phi^{-1}\left(\frac{N + 1 - i - \alpha}{N - 2\alpha + 2}\right) \tag{S16}$$

where Φ^{-1} is the inverse CDF for the unit Gaussian and $\alpha = 0.375$ (we note that the order statistics can be calculated numerically to high precision, which slightly improves the approximation). Therefore, in the large σ limit, we have

$$p_{\text{shared}}(\sigma, \rho) = 1 - \bar{F}_{\delta,\bar{a}_g}(\bar{0}) \tag{S17}$$

where the i-th component of $\bar{a}_g$ is given in Equation S16.

In the limit $\sigma \to 0$, the fitness values in the local neighborhood $\{a_i\}$ are uncorrelated variables drawn from the uniform distribution [-1,1] (where again we choose a zero mean distribution without loss of generality). In this case, the expected value of the order statistics for uniform variables leads to

$$a_i = \frac{2(N+2-i)}{(N+2)} - 1, \tag{S18}$$

and our approximate expression is therefore

$$p_{\text{shared}}(\sigma, \rho) = 1 - \bar{F}_{\delta, \bar{a}_u}(\bar{0}), \tag{S19}$$

where the i-th component of $\bar{a}_u$ is given in Equation S18.

Finally, the fraction of landscape pairs that share at least one maximum is given by

$$f_{\text{shared}} = 1 - (1 - p_{\text{shared}}(\sigma, \rho))^{N_{max}} \tag{S20}$$

The approximations in Equations S17-S20 are not exact, but we find that they agree quite well with results from simulated landscapes in the $\sigma = 0$ (low epistasis) and $\sigma = 1$ (high epistasis) cases (Figure 4A and 4B).

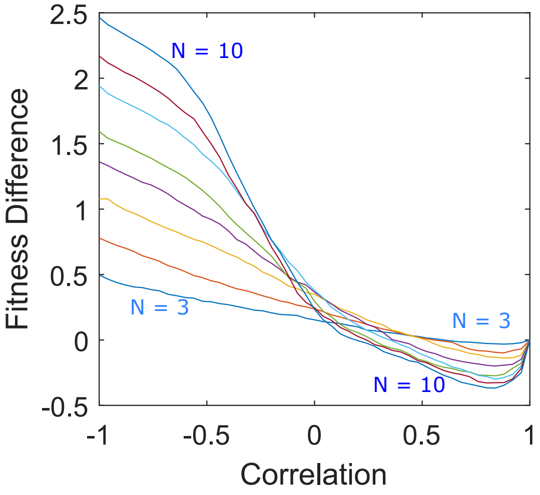

FIG. S1: **Rugged landscapes of different sizes show qualitatively similar changes in fitness as a function of correlation.** Difference in average fitness (at steady state) between populations adapted to a single static landscape (landscape A) or rapidly alternating landscape pairs (A-B cycles) as a function of correlation between landscapes A and B. Average fitness is defined as the mean fitness of the steady state genotype distribution (which arises following adaptation to either static or switching protocols) measured in landscape A. Different curves range from $N = 3$ to $N = 10$, and $\sigma = N/12$ for each landscape to achieve relatively similar magnitudes of epistasis as N varies.

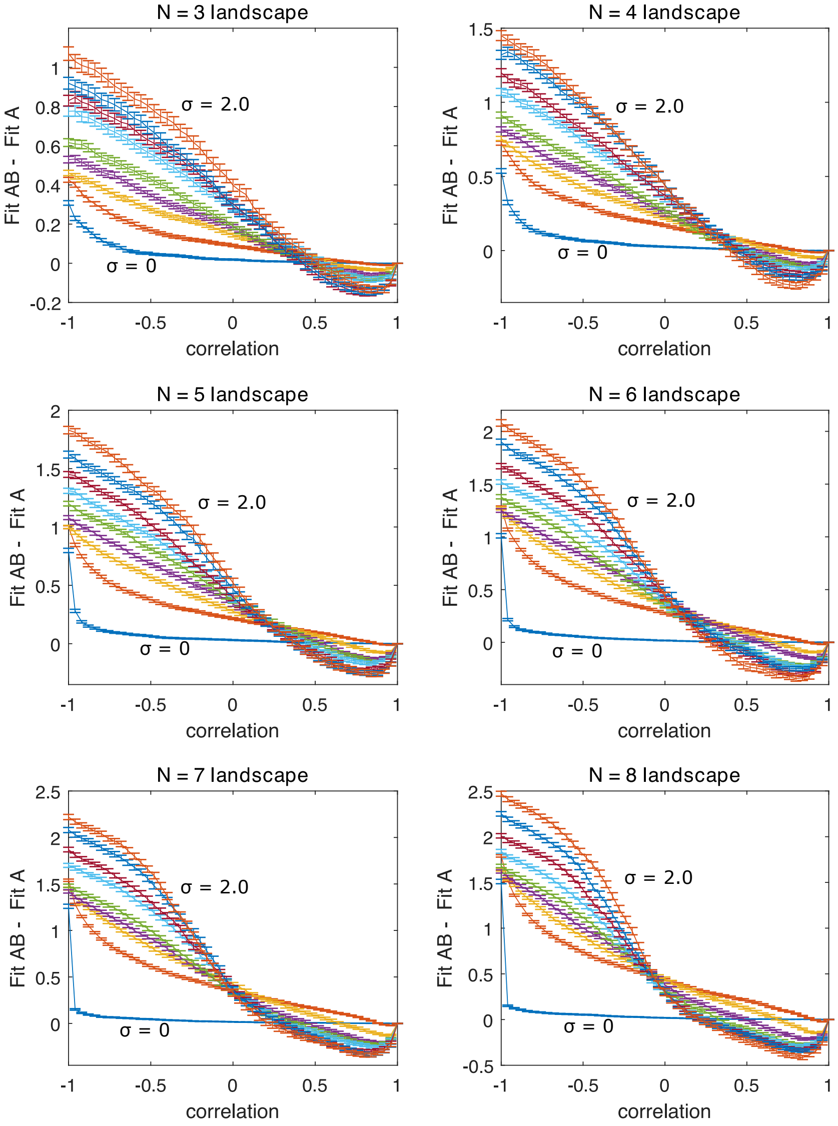

FIG. S2: **Landscapes of different sizes and sigmas show qualitatively similar results.** Difference in average fitness (at steady state) between populations adapted to a single static landscape (landscape A) or rapidly alternating landscape pairs (A-B cycles) as a function of correlation between landscapes A and B. Average fitness is defined as the mean fitness of the steady state genotype distribution (which arises following adaptation to either static or switching protocols) measured in landscape A. Different curves range from $\sigma = 0.0$ (blue, labeled) to $\sigma = 2.0$ (orange, labeled) in increments of 0.25 for each landscape. Error bars represent the standard error of the mean for each simulation.

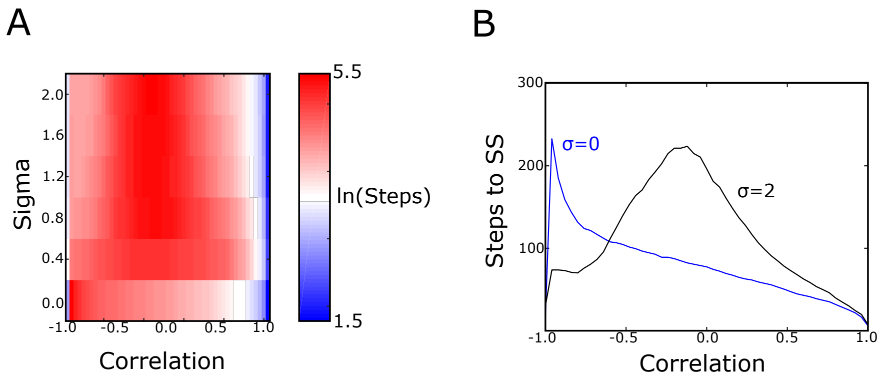

FIG. S3: **Adaptation to static and alternating environments approach steady state at different timescales.** A. Number of time steps (log scale) until steady state for alternating landscapes of a given ruggedness (σ) and correlation (ρ). Full correlated landscapes ($\rho = 1$) correspond to static evolution in a single landscape. B. Example slices through panel A corresponding to $\sigma = 0$ and $\sigma = 2$.

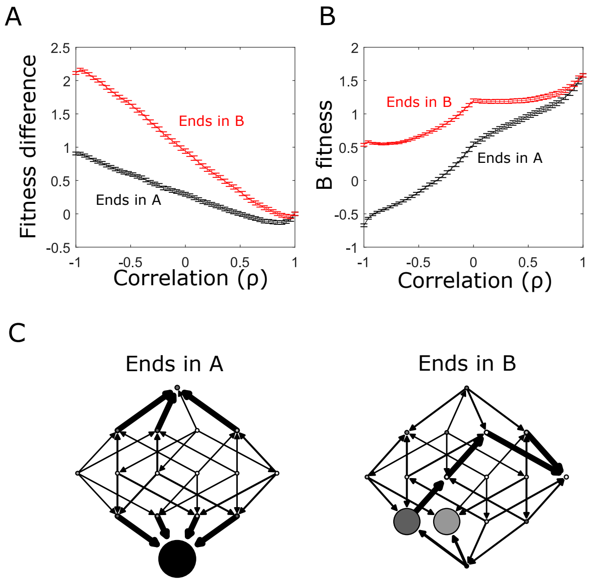

FIG. S4: **Adapted fitness depends on whether final step is taken in landscape A or B when landscapes are anticorrleated.** A. Difference in average fitness (at steady state) between populations adapted to a single static landscape (landscape A) or rapidly alternating landscape pairs (A-B cycles) as a function of correlation between landscapes A and B. Average fitness is defined as the mean fitness of the steady state genotype distribution (which arises following adaptation to either static or switching protocols) measured in landscape A. Curves correspond to steady state with a final step in landscape A (black) or a final step in landscape B (red). B. Collateral fitness change for populations adapted to alternating environments A and B as a function of inter-landscape correlation. Collateral fitness change is defined as the increase in average fitness in landscape B (relative to ancestor) associated with the steady state genotype distribution arising from adaptation to alternating A-B landscapes. C. Network representation of example fitness landscapes and transition probabilities following long-term adaptation to uncorrelated ($\rho = 0$) landscapes; adaptation ends either in landscape A (left) or B (right). $N = 4$ in all panels.

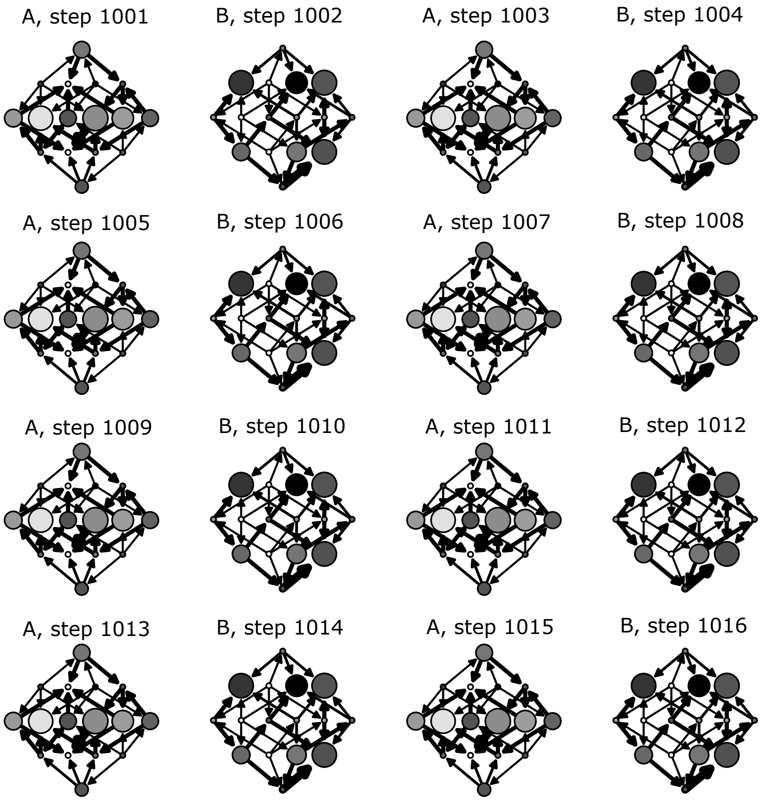

FIG. S5: **Adaptation to anti-correlated landscapes can produce cycles that sample large fractions of genotype space.** Network representations of 16 consecutive steps in the steady state for paired landscape evolution with $\rho = -0.88$. Each circle represents a genotype (ancestral genotype at the top), with shading indicating the relative fitness of that genotype and size representing the occupation probability at that time step. Arrows represent transitions between genotypes that occur with nonzero probability and are accessible starting from the ancestor genotype. The width of the arrow represents the magnitude of the transition probability.

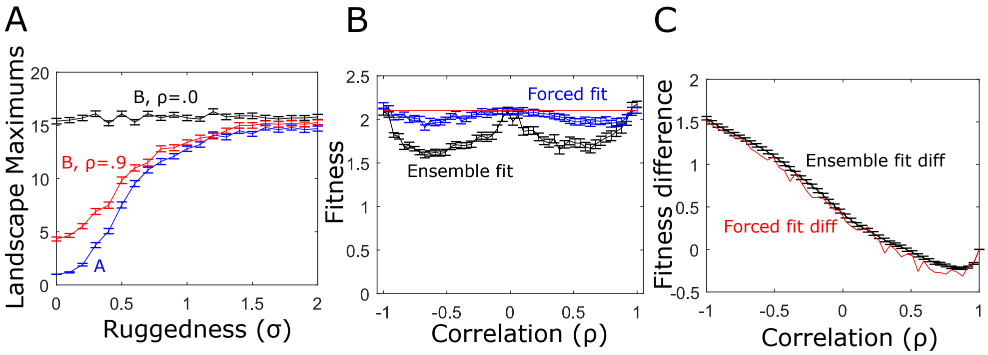

FIG. S6: **Statistical properties of landscape B differ from those of A but do not appreciably impact fitness differences between static and alternating landscapes.** A. Average number of local maxima in landscape A (blue) and two different B landscapes correlated with A to different degrees ($\rho = 0$, black; $\rho = 0.9$, red). B. Evolved fitness following static adaptation to landscape A (red) or B (black). Blue curve is fitness in a reduced "forced fit" ensemble of B landscapes, which includes only those B landscapes that lead to similar levels of fitness as in landscape A. C. Fitness difference between static and switching environments for the full paired landscape ensemble (black) and for the reduced "forced fit" ensemble (black).

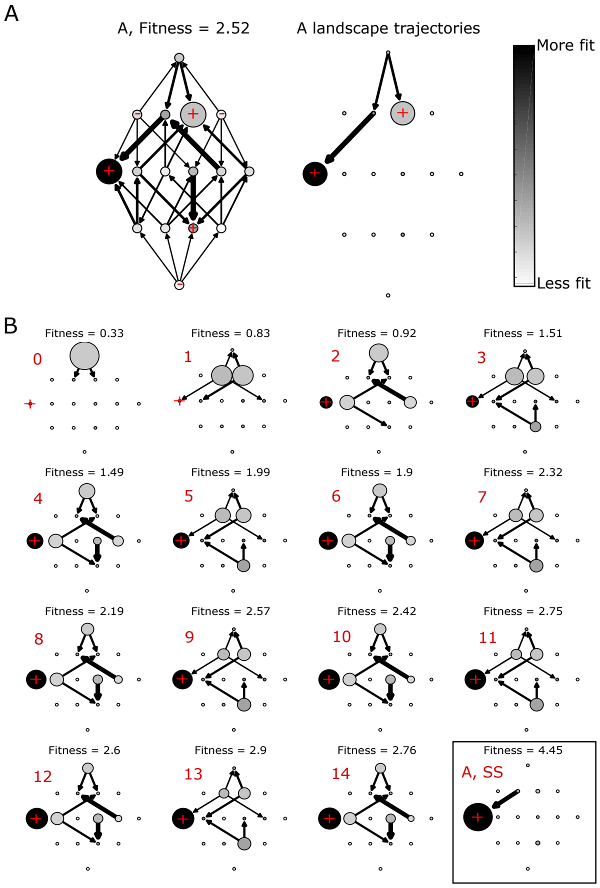

FIG. S7: **Evolutionary dynamics in alternating landscapes with positively correlated fitness peaks.** A. Left panel: network representation of adaptation on a static landscape (environment A) of size $N = 4$. Each circle represents a genotype (ancestral genotype at the top), with shading indicating the relative fitness of that genotype and size representing the occupation probability in the steady state. Red + symbols mark genotypes corresponding to local fitness maxima. Arrows represent transitions between genotypes that occur with nonzero probability–that is, the entries of the transition matrix. The width of the arrow represents the magnitude of the transition probability. Right panel: same as left panel, but showing only transitions that occur during adaptation starting from the ancestral genotype (top circle). B. Network representations of adaptation (at different time points) in alternating landscapes with positively correlated fitness peaks. Red number above each landscape represents the current evolutionary time point (ranging from 0 to SS, indicating steady state of approximately 200 steps). Directed arrows represent possible transitions between genotypes based on the current genotype distribution (indicated by the circle sizes) and the current landscape (A or B). Average fitness at each time point (calculated over the current genotype distribution) are listed above each plot. Even numbered steps correspond to landscape A, odd to landscape B.

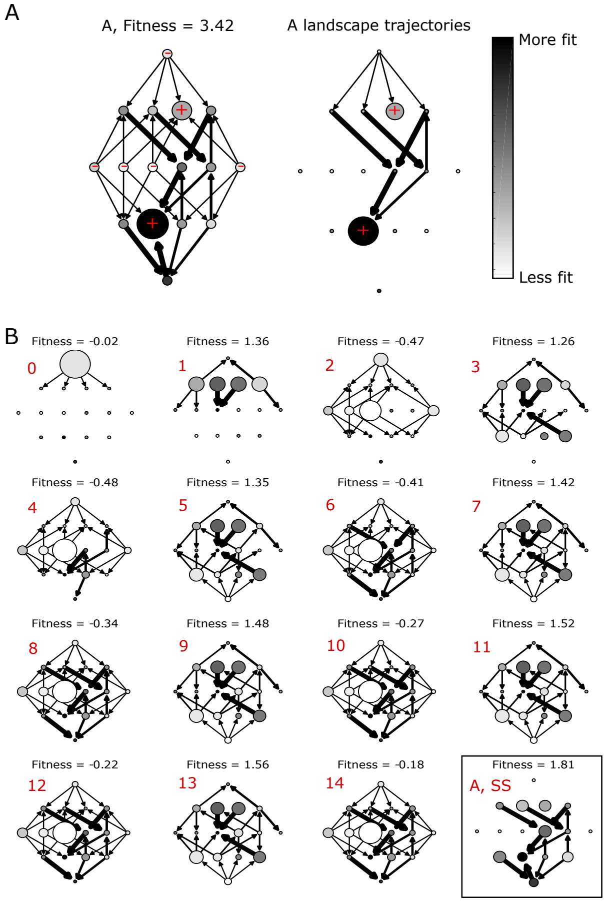

FIG. S8: **Evolutionary dynamics in alternating landscapes with negatively correlated fitness peaks.** A. Left panel: network representation of adaptation on a static landscape (environment A) of size $N = 4$. Each circle represents a genotype (ancestral genotype at the top), with shading indicating the relative fitness of that genotype and size representing the occupation probability in the steady state. Red + symbols mark genotypes corresponding to local fitness maxima. Arrows represent transitions between genotypes that occur with nonzero probability. The width of the arrow represents the magnitude of the transition probability. Right panel: same as left panel, but showing only transitions that occur during adaptation starting from the ancestral genotype (top circle). B. Network representations of adaptation (at different time points) in alternating landscapes with negatively correlated fitness peaks. Red number above each landscape represents the current evolutionary time point (ranging from 0 to SS, indicating steady state of approximately 200 steps). Directed arrows represent possible transitions between genotypes based on the current genotype distribution (indicated by the circle sizes) and the current landscape (A or B). Average fitness at each time point (calculated over the current genotype distribution) are listed above each plot. Even numbered steps correspond to landscape A, odd to landscape B.