Supporting Information for:
Genetic regulatory network motifs constrain adaptation through curvature in the landscape of mutational (co)variance

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1 Genotype-to-Phenotype equations

The equations in this section describe the "Genotype-to-Phenotype" map for the system of ODEs found in Figure 1 of the main text. They are in terms of genotypic values α_1 and α_2, which represent the summed additive contribution of both parental alleles for gene 1 and 2, respectively. Parameters are the amount of regulator needed to yield a 50% response (θ) and decay rate of expressed product (γ).

1.1 Motif "A" - single dependency, positive

$$x_1 = \frac{\alpha_1}{\gamma} \tag{S1}$$

$$x_2 = \frac{\alpha_1 \alpha_2}{\gamma(\theta + \alpha_1)} \tag{S2}$$

1.2 Motif "B" - single dependency, negative

$$x_1 = \frac{\alpha_1}{\gamma} \tag{S3}$$

$$x_2 = \frac{\theta \alpha_2}{\theta\gamma + \alpha_1} \tag{S4}$$

1.3 Motif "C" - double dependency, negative feedback loop

$$x_1 = \frac{2\theta\alpha_1}{(\theta\gamma - \alpha_1) + \sqrt{4\alpha_1\alpha_2 + (\theta\gamma + \alpha_1)^2}} \tag{S5}$$

$$x_2 = \frac{(\theta\gamma - \alpha_1) + \sqrt{4\alpha_1\alpha_2 + (\theta\gamma + \alpha_1)^2}}{2\gamma} \tag{S6}$$

1.4 Motif "D" - double dependency, both positive

$$x_1 = \frac{-\theta\gamma + \alpha_1 - \alpha_2 + \sqrt{4\theta\gamma\alpha_1 + (-\theta\gamma + \alpha_1 - \alpha_2)^2}}{2\gamma} \tag{S7}$$

$$x_2 = \frac{-\theta\gamma - \alpha_1 + \alpha_2 + \sqrt{4\theta\gamma\alpha_1 + (-\theta\gamma + \alpha_1 - \alpha_2)^2}}{2\gamma} \tag{S8}$$

1.5 Motif "E" - double dependency, both negative

$$x_1 = \frac{\alpha_1\alpha_2 - \theta^2}{\gamma(\theta + \alpha_2)} \tag{S9}$$

$$x_2 = \frac{\alpha_1\alpha_2 - \theta^2}{\gamma(\theta + \alpha_1)} \tag{S10}$$

1.6 Motif "F" - no dependency

$$x_1 = \frac{\alpha_1}{\gamma} \tag{S11}$$

$$x_2 = \frac{\alpha_2}{\gamma} \tag{S12}$$

2 Stability of equilibria

Stability of equilibrium values was determined by analyzing the eigenvalues of the Jacobian matrix for each system of ODEs. Below we provide the Jacobian and the eigenvalues. The real parts of each eigenvalue are negative for all motifs when genotypic values (α_1 and α_2) and expression levels (x_1 and x_2) are positive, indicating stable equilibrium phenotypes across genotypic values for all motifs.

2.1 Motif "A" - single dependency, positive

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & 0 \\ \frac{\alpha_2}{(\theta + x_2)^2} & -\gamma \end{pmatrix} \tag{S13}$$

$$\lambda_1, \lambda_2 = -\gamma \tag{S14}$$

2.2 Motif "B" - single dependency, negative

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & 0 \\ \frac{-\alpha_2 \theta}{(\theta + x_1)^2} & -\gamma \end{pmatrix} \tag{S15}$$

$$\lambda_1, \lambda_2 = -\gamma \tag{S16}$$

2.3 Motif "C" - double dependency, negative feedback loop

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & \frac{-\alpha_1 \theta}{(\theta + x_2)^2} \\ \frac{\alpha_2 \theta}{(\theta + x_1)^2} & -\gamma \end{pmatrix} \tag{S17}$$

$$\begin{aligned} \lambda_1, \lambda_2 \quad &= \{\pm \sqrt{-\alpha_1 \alpha_2 \theta^2 (\theta + x_1)^2 (\theta + x_2)^2} \\ &-\gamma \theta^4 - 2\gamma \theta^3 x_1 - 2\gamma \theta^3 x_2 - \gamma \theta^2 x_1^2 \\ &-4\gamma \theta^2 x_1 x_2 - \gamma \theta^2 x_2^2 - 2\gamma \theta x_1^2 x_2 \\ &-2\gamma \theta x_1 x_2^2 - \gamma x_1^2 x_2^2 \} \cdot ((\theta + x_1)(\theta + x_2))^{-1} \end{aligned} \tag{S18}$$

2.4 Motif "D" - double dependency, both positive

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & \frac{-\alpha_1 \theta}{(\theta + x_2)^2} \\ \frac{-\alpha_2 \theta}{(\theta + x_1)^2} & -\gamma \end{pmatrix} \tag{S19}$$

$$\begin{aligned} \lambda_1, \lambda_2 \quad &= \{\pm \sqrt{-\alpha_1 \alpha_2 \theta^2 (\theta + x_1)^2 (\theta + x_2)^2} \\ &-\gamma \theta^4 - 2\gamma \theta^3 x_1 - 2\gamma \theta^3 x_2 - \gamma \theta^2 x_1^2 \\ &-4\gamma \theta^2 x_1 x_2 - \gamma \theta^2 x_2^2 - 2\gamma \theta x_1^2 x_2 \\ &-2\gamma \theta x_1 x_2^2 - \gamma x_1^2 x_2^2 \} \cdot ((\theta + x_1)(\theta + x_2))^{-1} \end{aligned} \tag{S20}$$

2.5 Motif "E" - double dependency, both negative

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & \frac{\alpha_1 \theta}{(\theta + x_2)^2} \\ \frac{\alpha_2 \theta}{(\theta + x_1)^2} & -\gamma \end{pmatrix} \tag{S21}$$

$$\begin{aligned} \lambda_1, \lambda_2 \quad &= \{\pm \sqrt{-\alpha_1 \alpha_2 \theta^2 (\theta + x_1)^2 (\theta + x_2)^2} \\ &-\gamma \theta^4 - 2\gamma \theta^3 x_1 - 2\gamma \theta^3 x_2 - \gamma \theta^2 x_1^2 \\ &-4\gamma \theta^2 x_1 x_2 - \gamma \theta^2 x_2^2 - 2\gamma \theta x_1^2 x_2 \\ &-2\gamma \theta x_1 x_2^2 - \gamma x_1^2 x_2^2 \} \cdot ((\theta + x_1)(\theta + x_2))^{-1} \end{aligned} \tag{S22}$$

2.6 Motif "F" - no dependency

$$J(x_1, x_2) = \begin{pmatrix} -\gamma & 0 \\ 0 & -\gamma \end{pmatrix} \tag{S23}$$

$$\lambda_1, \lambda_2 = -\gamma \tag{S24}$$

3 Phenotype-to-Genotype equations

Below are equations that describe the "Phenotype-to-Genotype" map – equations that provide the genotypic values, calculated as the sum of parental allelic values, required to give a particular two-trait phenotype, given the parameters θ and γ.

3.1 Motif "A" - single dependency, positive

$$\alpha_1 = \gamma x_1 \tag{S25}$$

$$\alpha_2 = \frac{\gamma x_2(\theta + x_1)}{x_1} \tag{S26}$$

3.2 Motif "B" - single dependency, negative

$$\alpha_1 = \gamma x_1 \tag{S27}$$

$$\alpha_2 = \frac{\gamma_2(\theta + x_1)}{\theta} \tag{S28}$$

3.3 Motif "C" - double dependency, negative feedback loop

$$\alpha_1 = \frac{\gamma x_1(\theta + x_2)}{\theta} \tag{S29}$$

$$\alpha_2 = \frac{\gamma x_2(\theta + x_1)}{x_1} \tag{S30}$$

3.4 Motif "D" - double dependency, both positive

$$\alpha_1 = \frac{\gamma x_1(\theta + x_2)}{\theta} \tag{S31}$$

$$\alpha_2 = \frac{\gamma x_2(\theta + x_1)}{\theta} \tag{S32}$$

3.5 Motif "E" - double dependency, both negative

$$\alpha_1 = \frac{\gamma x_1(\theta + x_2)}{x_2} \tag{S33}$$

$$\alpha_2 = \frac{\gamma x_2(\theta + x_1)}{x_1} \tag{S34}$$

3.6 Motif "F" - no dependency

$$\alpha_1 = \gamma x_1 \tag{S35}$$

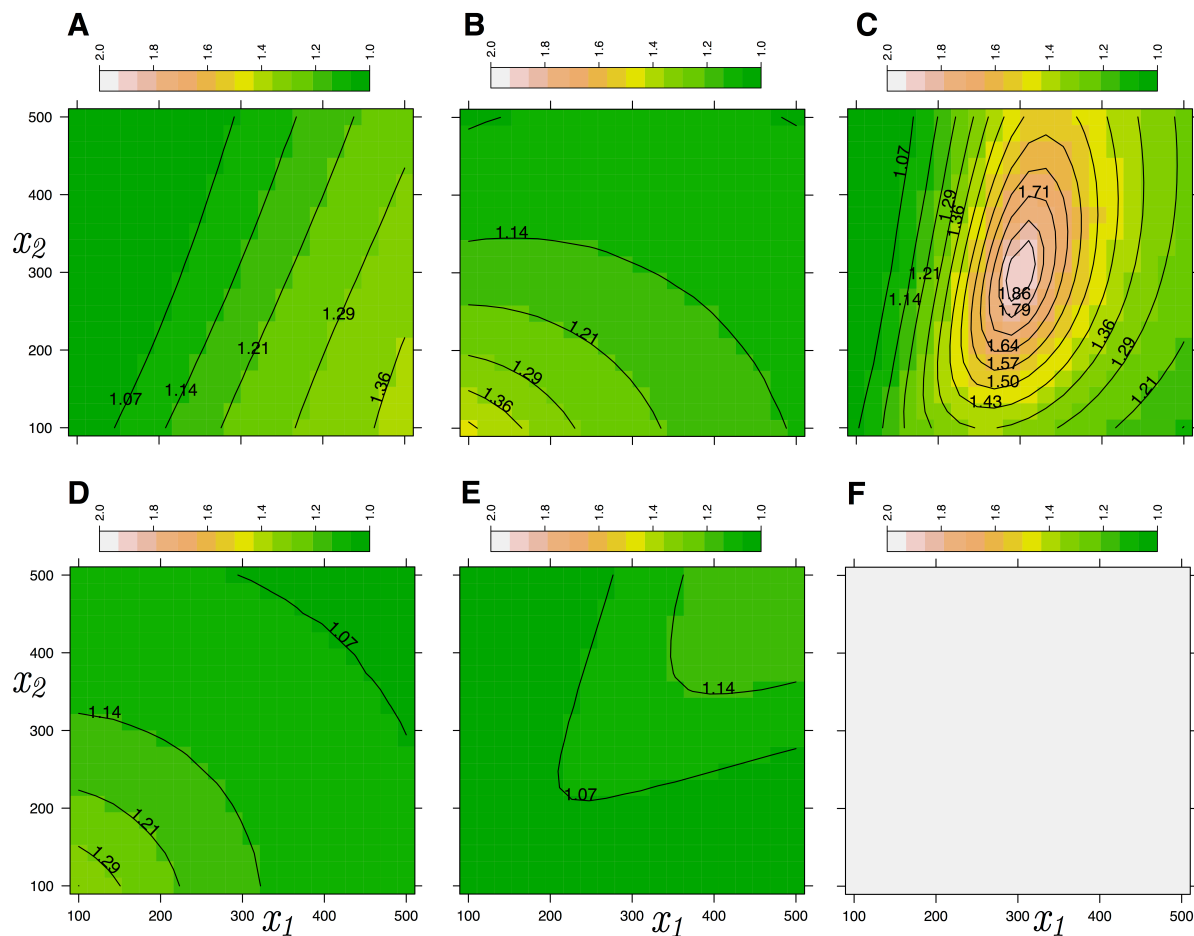$$\alpha_2 = \gamma x_2 \tag{S36}$$

4 Supplemental figures

Figure S1: Dimensionality of **M** across trait space. For each network motif (A-F), dimensionality was calculated as the sum of eigenvalues divided by the leading eigenvalue for each **M**-matrix along a 20-by-20 grid.
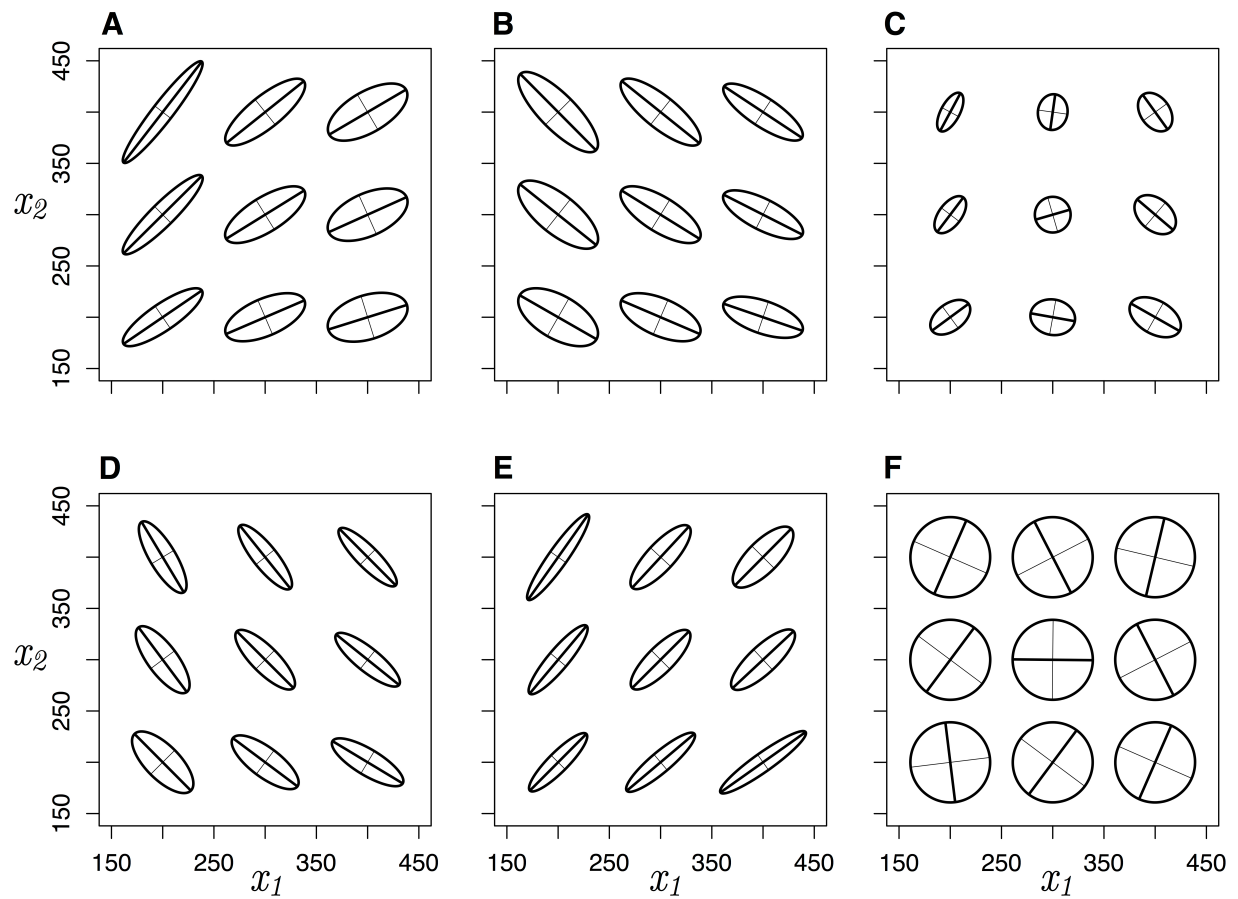
Figure S2: The additive genetic (co)variance matrix **G** across phenotypic space. For each network motif (A-F), **G** matrices for nine populations are plotted as 95% confidence ellipses of breeding values (i.e., posterior mode of individual's random effects for each trait).

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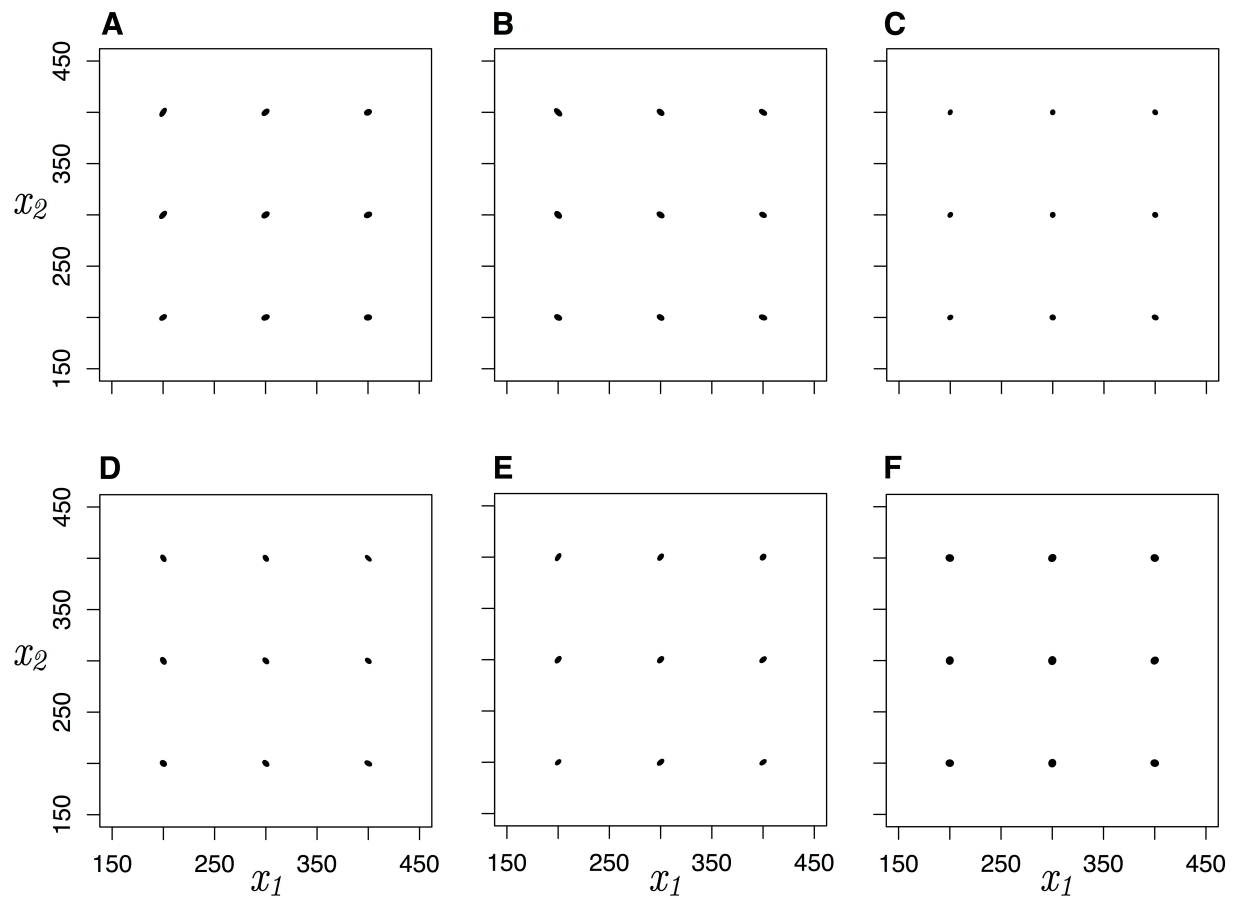
Figure S3: The epistatic (co)variance matrix **E** across phenotypic space. For each network motif (A-F), **E** matrices for nine populations are plotted as 95% confidence ellipses of the posterior mode of individual's residual effects for each trait.
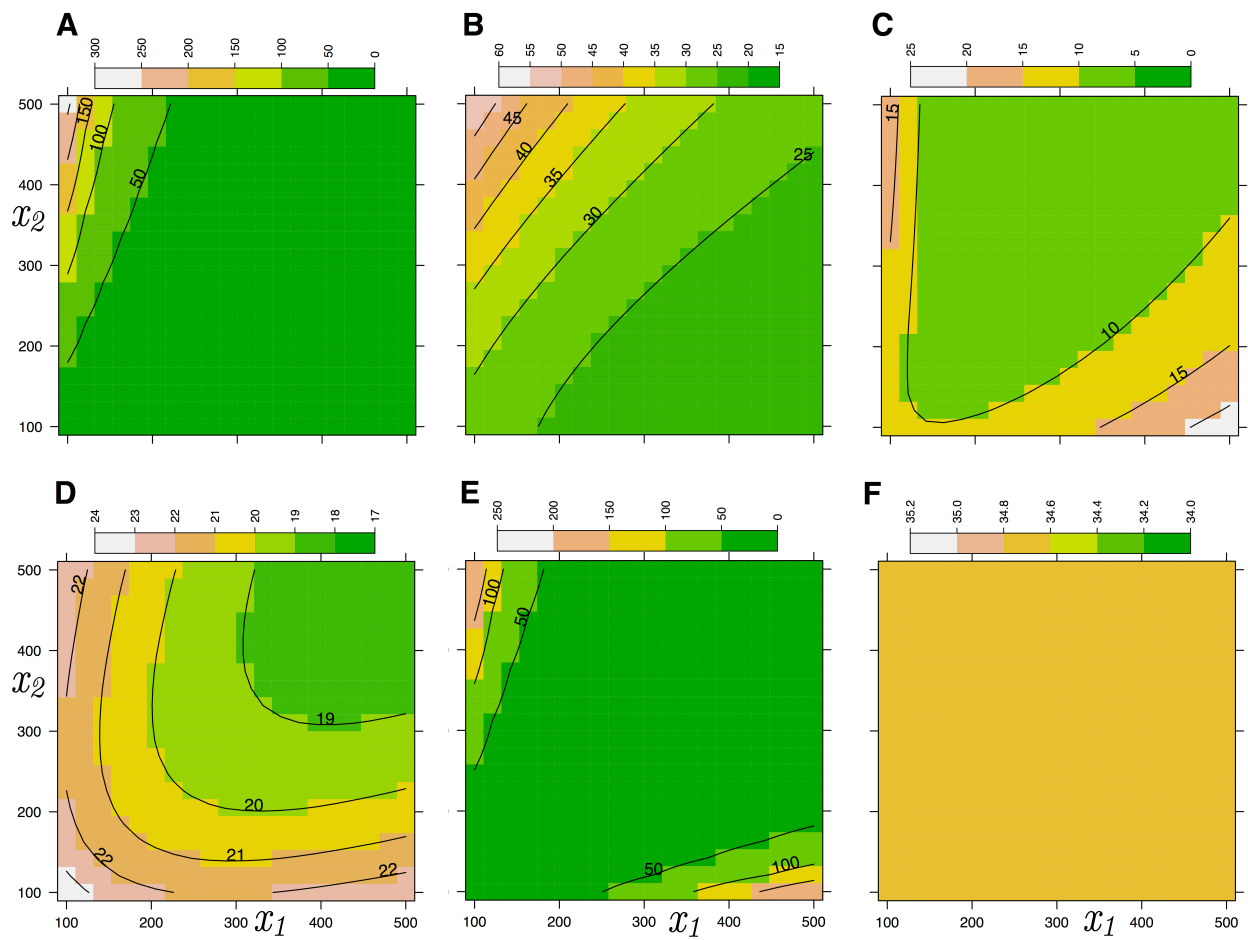
Figure S4: Evolvability across trait space when mutation is limiting. For each network motif (A-F), evolvability was calculated as the average of the eigenvalues of **M**. Note that the scales are different across panels.
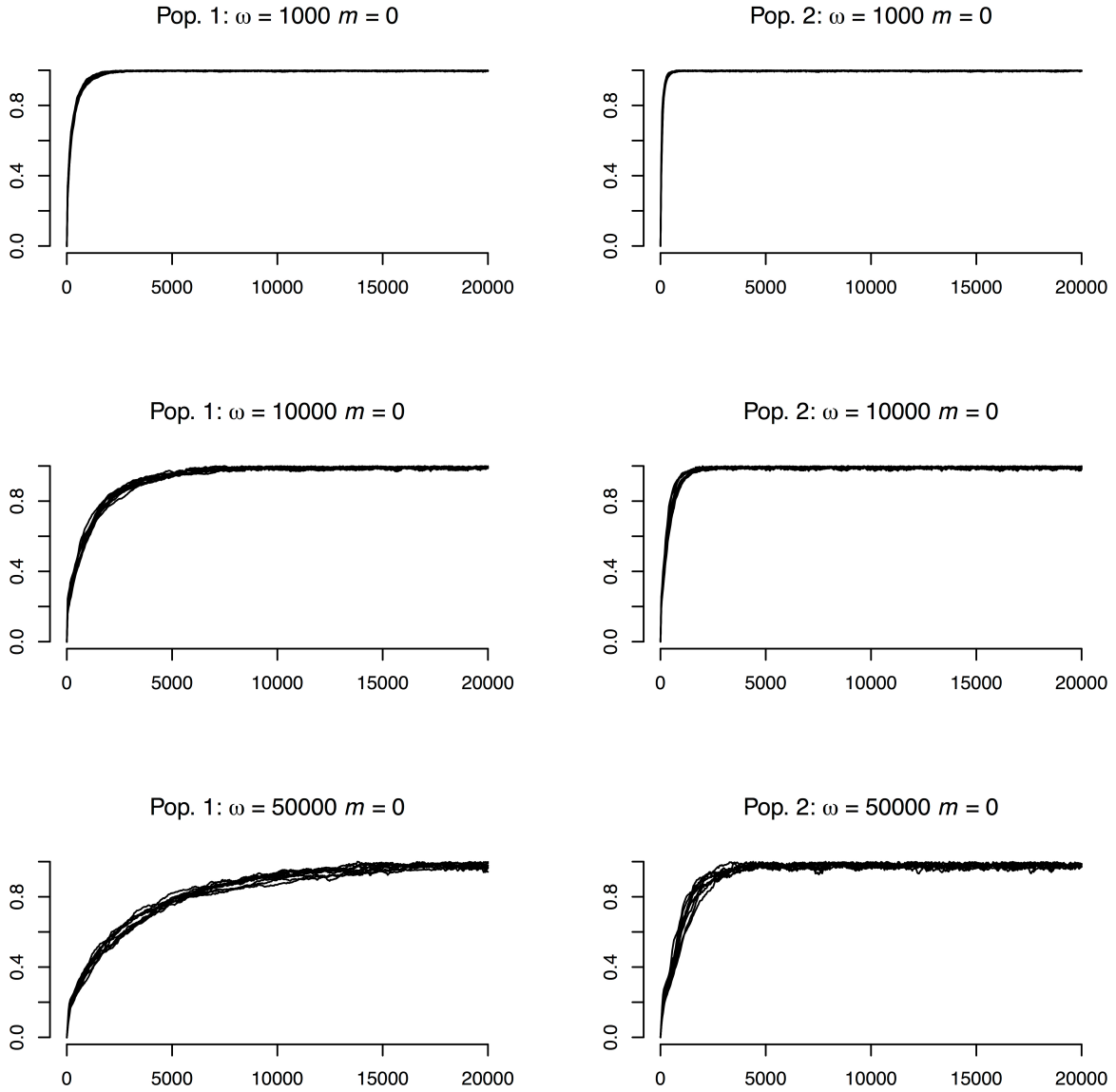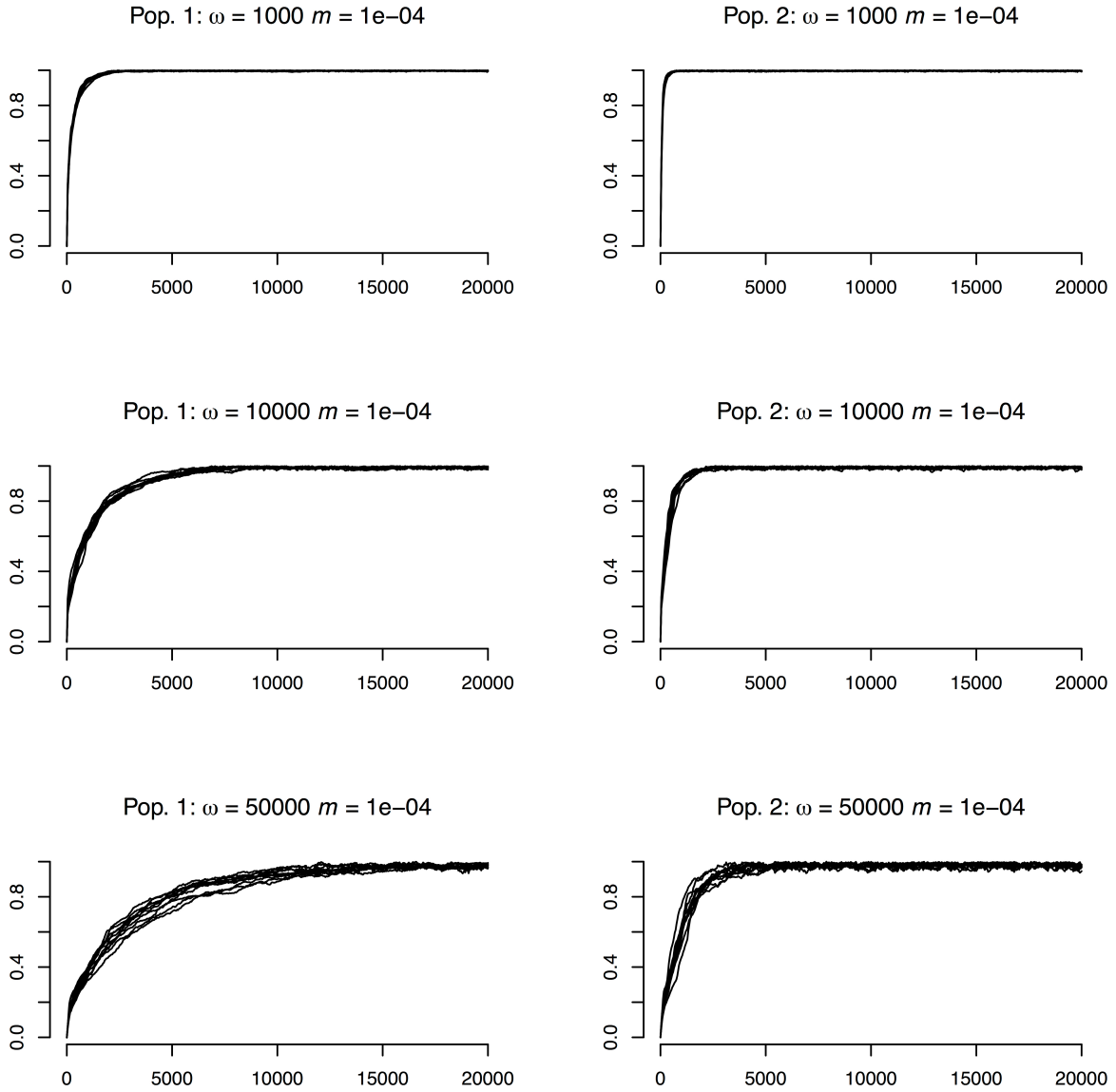
Figure S5: The extent of local adaptation through time across 15 simulated replicates for Population "1" (left column) and "2" (right column). Rows denote seperate variance of stabilizing selection, ω. Shown here are data from migration = 0.
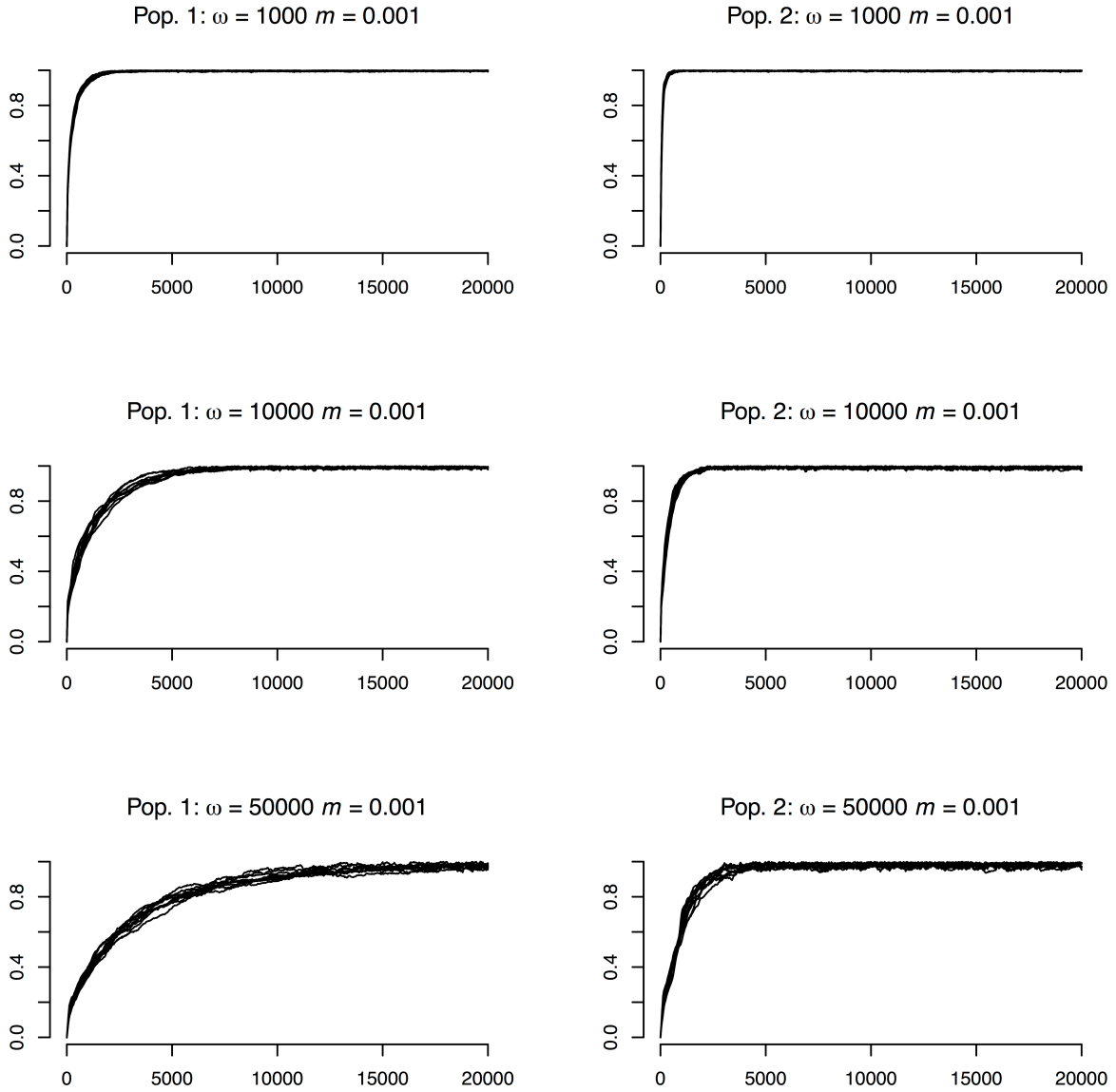
Figure S6: The extent of local adaptation through time across 15 simulated replicates for Population "1" (left column) and "2" (right column). Rows denote seperate variance of stabilizing selection, ω. Shown here are data from migration = 0.0001.
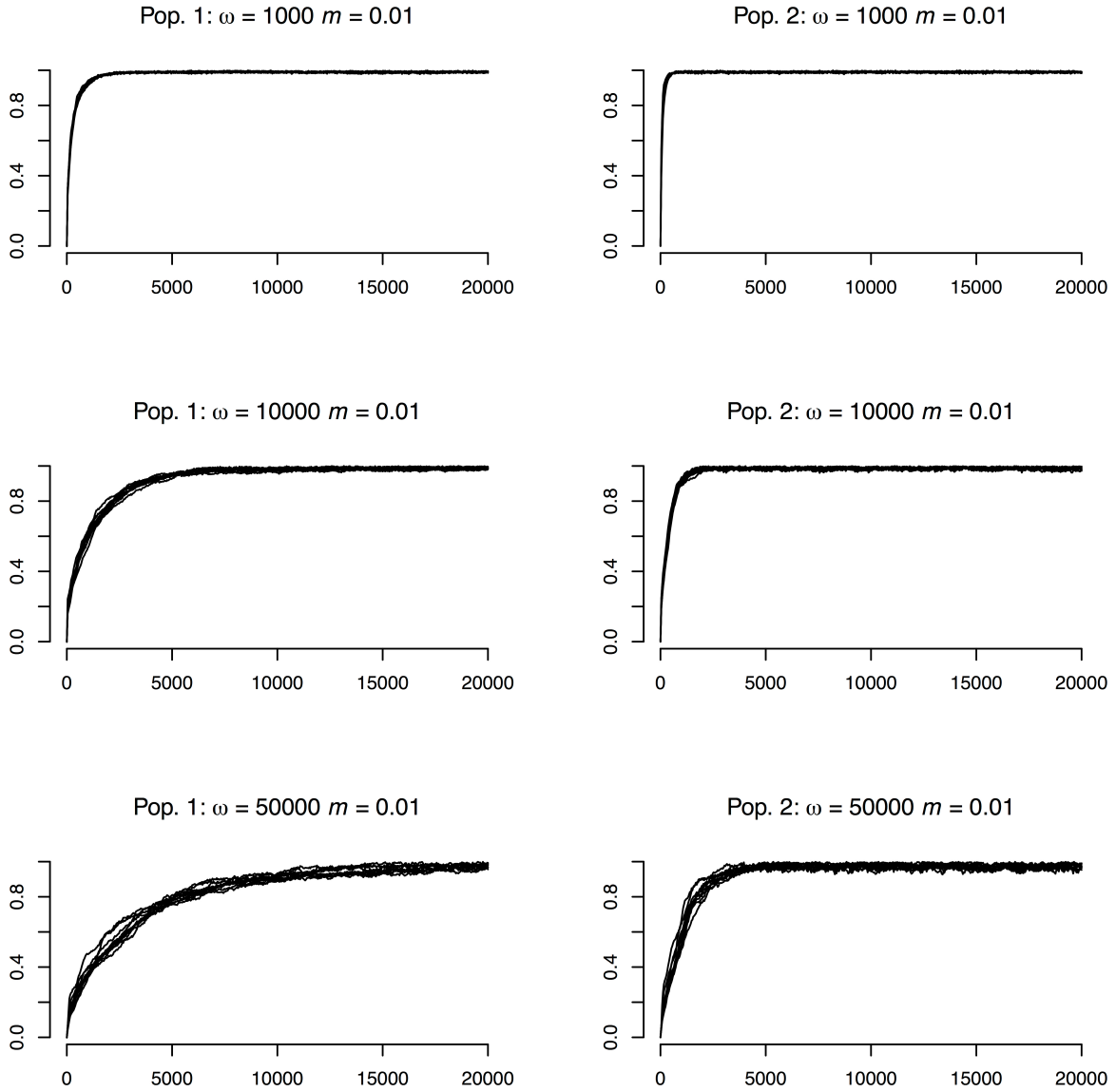
Figure S7: The extent of local adaptation through time across 15 simulated replicates for Population "1" (left column) and "2" (right column). Rows denote seperate variance of stabilizing selection, ω. Shown here are data from migration = 0.001.

Figure S8: The extent of local adaptation through time across 15 simulated replicates for Population "1" (left column) and "2" (right column). Rows denote seperate variance of stabilizing selection, ω. Shown here are data from migration = 0.01.
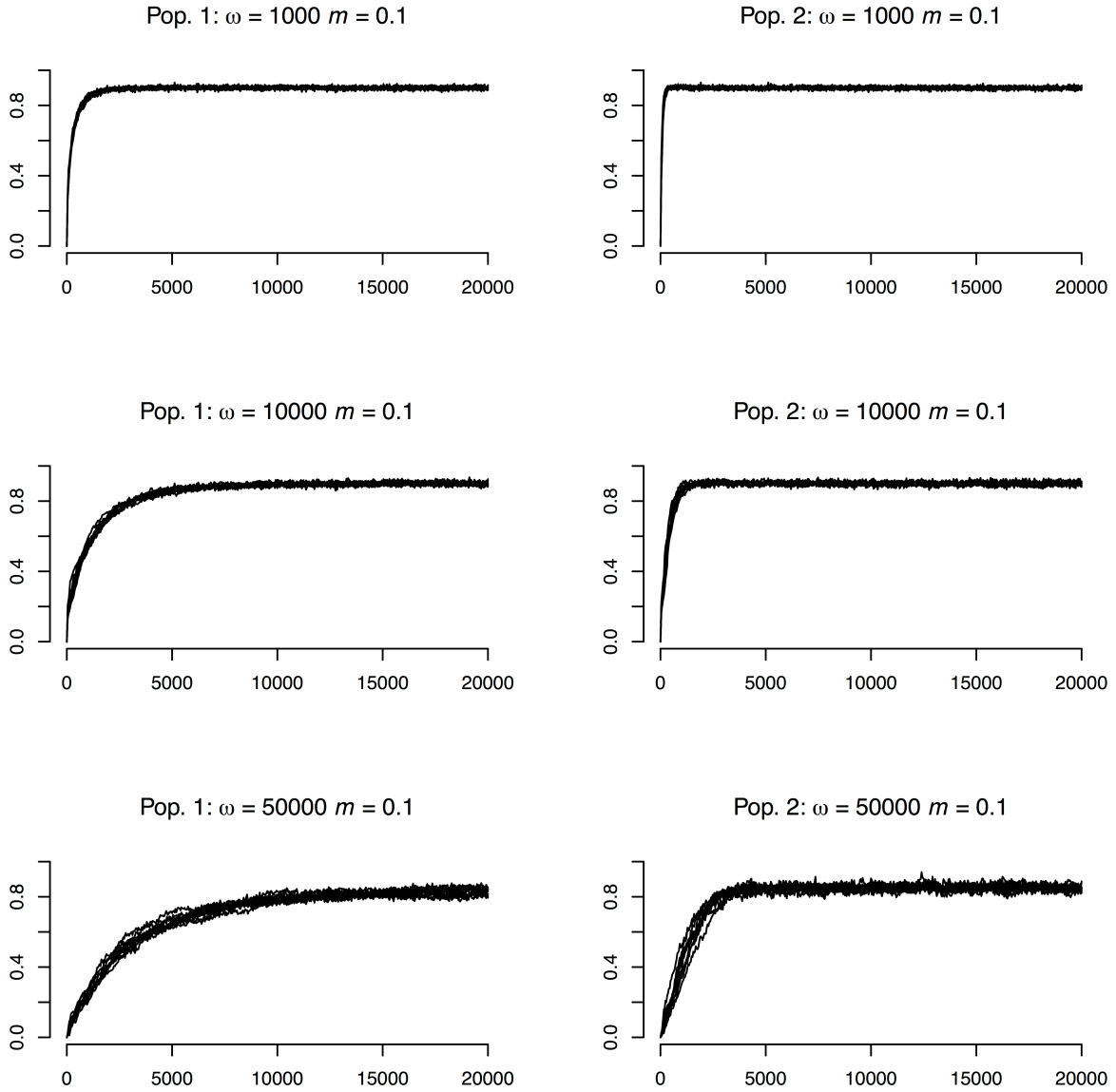
Figure S9: The extent of local adaptation through time across 15 simulated replicates for Population "1" (left column) and "2" (right column). Rows denote seperate variance of stabilizing selection, ω. Shown here are data from migration = 0.1.