SUPPLEMENTARY MATERIAL

Comparison of approximate and exact results in one-locus model: In order to verify the validity and accuracy of the approximate equilibria reported in the main text, I solved the exact (non-approximated) equations. This yielded three solutions; for each parameter set shown, I chose the solution that yielded real results between 0 and 1. In addition, I found numerical equilibria by solving the equations numerically under a variety of parameter values at generation 10^7. Fig. S1 shows these exact results compared to the approximate solutions derived in the main text.

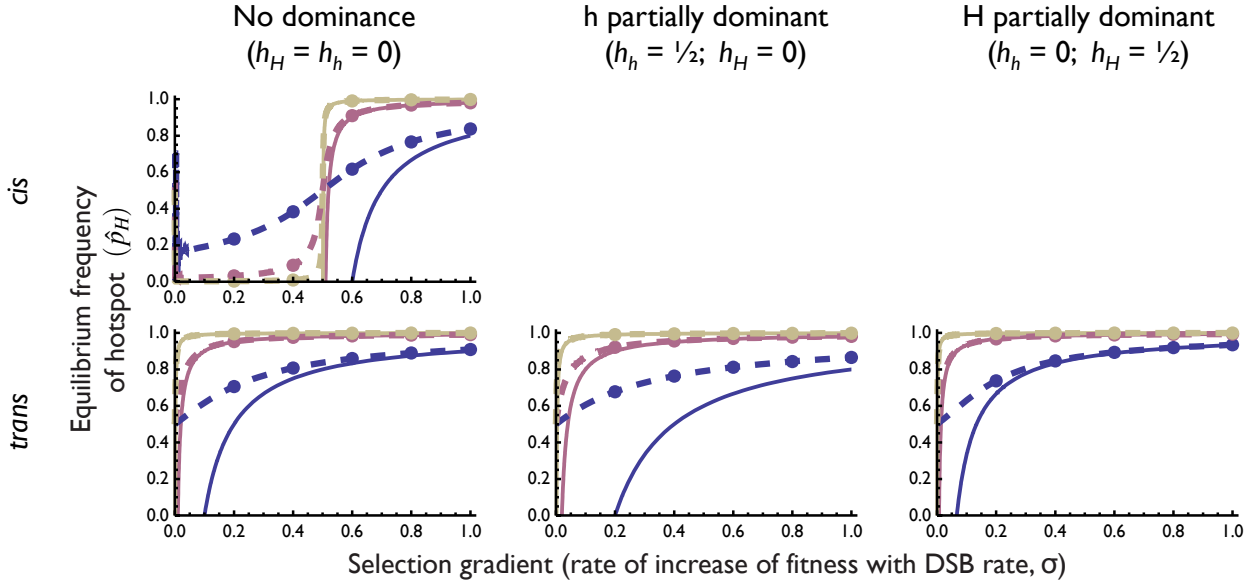

Fig. S1: Comparison of approximate "near-fixation" equilibria with exact and numerical equilibria for *cis* control (with no dominance) and *trans* control (with no dominance or one control allele partially dominant). Thin, solid lines show approximate results as shown in Fig. 2 of the main text. Thick, dashed lines show exact result, determined by solving exact equations and choosing the solution (out of three possibilities) that yielded real results between 0 and 1 for the given valid parameter values. Circles show equilibria achieved when the exact equations are solved numerically, starting from $p_H = 0$, at generation 10^7. As expected, the approximate solutions fit particularly well when selection is strong (σ or β_H high) and therefore the exact solution is near $p_H = 1$.

Other parameters are as for Fig. 2 in the main text: color/lightness represents the conversion

rate of the hot allele (β_H) — blue/dark: $\beta_H = 10^{-6}$; pink/medium: $\beta_H = 10^{-5}$; yellow/light: $\beta_H = 10^{-4}$ Higher DSB rates ($\beta_H > 10^{-4}$) closely resemble the pattern for $\beta_H = 10^{-4}$. Other parameter values: $\mu = \nu = 10^{-7}$.

Analysis of two-locus modifier model: I substituted the frequency of haplotype *hm* (p_{hm}) with $1 - (p_{\mathrm{HM}} + p_{\mathrm{Hm}} + p_{\mathrm{hM}})$ and analyzed the system of three differential equations describing the changes in frequency of haplotypes *Hm*, *hM*, and *HM:*

$$\frac{dp_{\mathrm{Hm}}}{dt} = \frac{d_s p_{\mathrm{Hm}}}{dt} + \frac{d_m p_{\mathrm{Hm}}}{dt} + \frac{d_c p_{\mathrm{Hm}}}{dt} + \frac{d_r p_{\mathrm{Hm}}}{dt} \tag{1}$$

$$\frac{dp_{\mathrm{hM}}}{dt} = \frac{d_s p_{\mathrm{hM}}}{dt} + \frac{d_m p_{\mathrm{hM}}}{dt} + \frac{d_c p_{\mathrm{hM}}}{dt} + \frac{d_r p_{\mathrm{hM}}}{dt} \tag{2}$$

$$\frac{dp_{\mathrm{HM}}}{dt} = \frac{d_s p_{\mathrm{HM}}}{dt} + \frac{d_m p_{\mathrm{HM}}}{dt} + \frac{d_c p_{\mathrm{HM}}}{dt} + \frac{d_r p_{\mathrm{HM}}}{dt} \tag{3}$$

The resident population is assumed to be fixed for allele m ($p_{\mathrm{hm}} = p_{\mathrm{Hm}} = 0$), with the H allele at equilibrium ($p_{\mathrm{Hm}} = \hat{p}_H$); a description of the frequency of haplotype *Hm* (Equation 1) is therefore a complete description of the resident population, while Equations 2 and 3 describe the dynamics of the modifier allele.

I verified that the system is in equilibrium ($\frac{dp_{\mathrm{Hm}}}{dt} = \frac{dp_{\mathrm{hM}}}{dt} = \frac{dp_{\mathrm{HM}}}{dt} = 0$) under the two types of resident population of interest: (1) a population fixed for the m allele and in mutational equilibrium at the **H** locus ($\hat{p}_H = \frac{\nu}{\nu+\mu}$); and (2) a population fixed for the m allele and at arbitrary frequency $p_{Hm,0}$ at the **H** locus, but with no mutation ($\mu = \nu = 0$). Given equilibrium, the leading eigenvalue of the mutant submatrix of the Jacobian matrix (a matrix made up of the first derviatives of each function with respect to each variable, in this case the chromosome frequencies, evaluated at the relevant equilibrium) describes the rate of spread of the mutant allele (Otto and Day 2007). Below, I calculate these eigenvalues separately for population types (1) and (2), approximating using Taylor expansion under the assumptions that μ, ν, β_h, and $\beta_H - \beta_h$ are small ($O[\zeta], \zeta << 1$).

Resident population at mutational equilibrium ($\hat{p}_H = \frac{\nu}{\nu+\mu}$). The two approximate eigenvalues of the mutant submatrix are:

$$\lambda_1 = \frac{\mu^2 + \nu^2 + \nu\left(r + \frac{\beta_1}{2} - \frac{\tau\beta_1}{2}\right) + \mu\left(r + 2\nu + \frac{\beta_1}{2} - \frac{\tau\beta_1}{2}\right)}{\mu + \nu} \tag{4}$$

and

$$\lambda_2 = \frac{\nu\left(\sigma\left(1 - h_m + h_M\right) - \frac{\tau}{2}\left(1 - h_m - h_M\right)\right)\left(\beta_H - \beta_h\right)}{\mu + \nu} \tag{5}$$

Using the approximation described above, $\lambda_1 > \lambda_2$ when $2r(\mu + \nu) < 0$; *i.e.*, never. λ_2 is therefore the leading eigenvalue, and describes the initial rate of change of the modifier. The consequences of this are discussed in the main text and Table 3 of the text..

Resident population at arbitrary frequency $p_{Hm,0}$ ($\mu = \nu = 0$). The two approximate eigenvalues of the mutant submatrix are:

$$\begin{aligned}\lambda_1 = \beta_H\left(\sigma - \frac{1 - (1-2\sigma)h_m}{2}\right) - \beta_h\left(\sigma - \frac{\tau - (1-2\sigma)h_m}{2}\right) \\ - p_{\mathrm{Hm},0}\left(\left(\beta_H - \beta_h\right)\left(\sigma - \frac{1 - (1-2\sigma)h_m + (2\sigma+\tau)h_M}{2}\right)\right) - r\end{aligned} \tag{6}$$

and

$$\lambda_2 = p_{\mathrm{Hm},0}\left(\sigma\left(1 - h_m + h_M\right) - \frac{\tau}{2}\left(1 - h_m - h_M\right)\right)\left(\beta_H - \beta_h\right) \tag{7}$$

Under the approximations described above, λ_1 is the leading eigenvalue ($\lambda_1 > \lambda_2$) if

$$r < -\frac{(1-\tau)\beta_0 + \left(1 - h_m\right)\left(\beta_H - \beta_h\right)\left(1 - 2\sigma + p_{\mathrm{Hm},0}(4\sigma - 1 - \tau)\right)}{2} \tag{8}$$

This occurs only when r is small, and even then only when either (a) selection is relatively weak ($\sigma < \frac{1+\tau}{4}$) if the initial frequency of allele H is high ($p_{\mathrm{Hm},0} > \frac{1-2\sigma}{1-4\sigma+\tau}$) or (b) selection is relatively strong ($\sigma > \frac{1+\tau}{4}$) if the initial frequency of allele H is low ($p_{\mathrm{Hm},0} < \frac{1-2\sigma}{1-4\sigma+\tau}$). Graphical exploration suggests Condition 8 is only met when $r <\sim 5 \times 10^{-3}$ for relevant parameter values. In addition, under the approximations described above, the value of σ at which λ_1 becomes positive is always

greater than the value at which λ_2 becomes positive. λ_2 is therefore the eigenvalue that determines the invasion conditions. The consequences of this are discussed in the main text and Table 3.

LITERATURE CITED

OTTO, S. P. and T. DAY, 2007 *A biologist's guide to mathematical modeling in ecology and evolution*. Princeton, NJ: Princeton University Press.