



Figure S2 (Caption next page.)

Figure S2 (Previous page.) Median net F2 hybrid misregulation of the positively selected trait under varying selection strengths ($1/\sigma_s^2$) and mutation-effect sizes in the pleiotropic (clear boxes) and two-domain (gray boxes) models. (A and B) 12-bit motif, which yields a larger mutation effect size. (C and D) 24-bit motif, which yields a smaller mutation effect size. Selection strengths correspond to the steepness of the fitness function around P_{opt} (equation 2), and are expressed as multiples (0.125–8) of $1/\sigma_s^2$, where at baseline, the tolerance $\sigma_s^2 = 2.5 * 10^{-3}$. The strength of selection at the positively selected trait has no effect. Selection strength at the conserved trait has no effect in the two-domain control model, but increasingly constrains misregulation in the pleiotropic model as selection strength increases. The constraints on the evolution of misregulation are not quite as strong as in the 12-bit case. Marginal fitnesses depend on $1/\sigma_s^2$ and are not shown. Box plots show medians, quartiles and full ranges. Simulation conditions as in text Figure 4.