



**Figure S6: Four ways in which misregulation can affect adaptive gene expression in a new state or environment. (Analogous to Figure 3 but for  $p_B = 0.45$ ,  $f^O = G_{on}/G = 0.5$ .)** The four panels show contour plots of four different quantities as a function of the fraction  $f^N$  of genes that must be expressed for optimal adaptation in the new state (horizontal axes), and as a function of the expression correlation  $c$  between the old and new state (vertical axes). These quantities are **A)** the change in the fraction  $\Delta f_{11}^m$  (eq. 2) of correctly 'on' genes under misregulation; **B)** the change in the fraction  $\Delta f_{00}^m$  (eq. 3) of correctly 'off' genes under misregulation; **C)** the change in the fraction  $\Delta f_{00}^m + \Delta f_{11}^m$  (eq. 4) of all correctly expressed genes under misregulation; **D)** the change in mean fitness in the new state under misregulation, expressed as  $r_w - 1 = (w^N/w^N|_{m-}) - 1$  (eq. 5). These quantities do not only depend on  $f^N$  and  $c$ , but also on the excess  $\Delta_m = f_{01}^O - f_{10}^O$  of incorrectly on genes in the old state, which I obtained through computer simulations of the evolutionary dynamics of misregulation (Methods). These simulations are based on populations with  $N_e = 10^3$  individuals,  $G = 1500$  loci,  $G_{on} = 750$  and thus  $f^O = G_{on}/G = 0.45$ ,  $p_B = 0.25$ ,  $s_{01} = 0.1/N_e$ ,  $s_{10} = 10/N_e$ , as estimated from empirical data (Kim et al. 2009; Mustonen and Lassig 2005; Mustonen et al. 2008; Hahn et al. 2003), a mutation rate per nucleotide of  $\mu = 10^{-5}$ , and an incidence of mutations leading to the destruction or creation of binding sites estimated from mouse PBM data, as described in Methods. I initialized populations with no misregulation for each individual ( $f_{01} = f_{10} = 0$ ), and continued the simulations for  $1/\mu$  generations, because preliminary simulations (not shown) had indicated that populations reach equilibrium by then. After  $1/\mu$  generations, I calculated the population average of  $f_{01}$  and  $f_{10}$  over 100 generations. I used this average to compute  $\Delta_m = f_{01}^O - f_{10}^O$  for all panels.