



**Figure S2** Effect of genotypic divergence on median net F2 hybrid misregulation and corresponding fitness under directional selection. Genotypic divergence is represented by the number of substitutions required to evolve between the optimal phenotypes at the beginning and end of the selection period. Bioenergetic parameters specifying the G-P map were held constant and only the initial optimal phenotype was varied. (A) Evolving towards intermediate phenotype (final  $P_{opt} = 0.5$ ). (B) Evolving towards extreme phenotype (final  $P_{opt} = 1.0$ ). Hybrid fitness follows equation 4. Note the different scales. Box plots show median, quartiles and full ranges.