

File S3: A lower analytical bound for the incidence of misregulation when mutations are very rare and selection is strong.

Selection against misregulation will reduce the incidence of misregulation caused by mutation. Consider first binding sites for the G_{on} genes that need to be active, and assume that mutations destroy any such binding site at a rate μ_1^- , and create a new binding site at a rate μ_1^+ . An inactivated binding site reduces fitness by s_{10} . I will assume that $s_{10} > \mu_1^-, \mu_1^+$. When mutations are sufficiently rare that they introduce few new alleles into a population per generation, binding sites effectively evolve independently from each other, and reach a mutation selection balance where $\hat{f}_{10} = (\mu_1^-/s_{10})f^O$ (Ewens, 2012, p. 15). Likewise, for the G_{off} genes that need to be inactive, assume that mutations create active binding sites at rate μ_0^+ and destroy them at rate μ_0^- . For $s_{01} > \mu_0^-, \mu_0^+$ we get $\hat{f}_{01} = (\mu_0^+/s_{01})(1 - f^O)$. These equilibria hold for infinite and finite populations and are independent of population size (Ewens, 2012, 5.73). They can be considered lower bounds for the incidence of misregulation, reached when mutation is weak and selection is strong. Specifically, they may apply when much less than one binding site is mutated in each population per generation, i.e., if $N_e L \mu G \ll 1$, otherwise individuals with deleterious mutations at multiple binding sites may segregate in the population.

References

Ewens, W. J. (2012). *Mathematical population genetics 1: Theoretical introduction*, Volume 27. New York, NY: Springer Science & Business Media.