Cooperativity Enhances Mutational Robustness of a Negative Autoregulation Transcription Factor

David C. Marciano\textsuperscript{1*}, Rhonald C. Lua\textsuperscript{1*}, Christophe Herman\textsuperscript{1}, & Olivier Lichtarge\textsuperscript{1,2,3}

(1) Molecular \& Human Genetics, Baylor College of Medicine (2) Verna \& Marrs McLean Department of Biochemistry \& Molecular Biology, Baylor College of Medicine (3) Computational \& Integrative Biomedical Research Center, Baylor College of Medicine; * These authors contributed equally

Biological systems are known to be robust to external perturbations and intrinsic fluctuations. In the bacterium \textit{Escherichia coli}, transcriptional factors often repress their own expression to form a negative-feedback network motif that enables robustness to changes in biochemical parameters. However, the response of negative feedback networks to deleterious mutations in the transcription factor have not been treated theoretically and tested experimentally. Here we present a simple phenomenological model of a negative feedback transcription factor repressing both itself and another target gene. Analysis of the model shows that the target gene levels are robust to mutations of the transcription factor, and that the robustness improves as the degree of cooperativity in self-repression increases (modeled as a Hill coefficient). The prediction is tested in the LexA transcriptional network of \textit{E. coli} by altering cooperativity of the system. Indeed, the robustness of target gene expression to deleterious mutations in LexA is dependent upon the Hill coefficient of the negative feedback system. Considering the proposed importance of gene regulation in speciation, parameters governing a transcription factor's robustness to mutation may have significant influence on an organism's capacity to evolve.