

EVOLUTIONARY LOSS AND REGAIN OF GENE NETWORK FUNCTION

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ABSTRACT

Natural or synthetic genetic modules can lose their biological function over long-term evolution if that function is costly. How populations can evolve to restore such broken biological function is poorly understood. To test the reversibility of evolutionary breakdown, we use a synthetic positive-feedback (PF) gene circuit integrated into haploid *Saccharomyces cerevisiae* cells. In previous evolution experiments, mutations in a gene eliminated the fitness costs of PF activation, corrupting gene circuit function. Since PF activation can provide drug resistance, we grew such corrupted mutants in both drug and inducer, imposing selection to develop drug resistance and possibly regain PF function. We observe three distinct adaptation scenarios with or without repairing lost gene circuit function. The data suggest unexpected interactions between intracellular gene network dynamics and evolutionary dynamics. These results highlight how an evolutionary parameter, such as the growth rate, can connect regulatory network dynamics with evolutionary dynamics, which has important consequences for understanding the evolution of drug resistance and developing future synthetic biology applications.

Keywords: evolution, gene circuit, positive feedback, bistability, regain of function