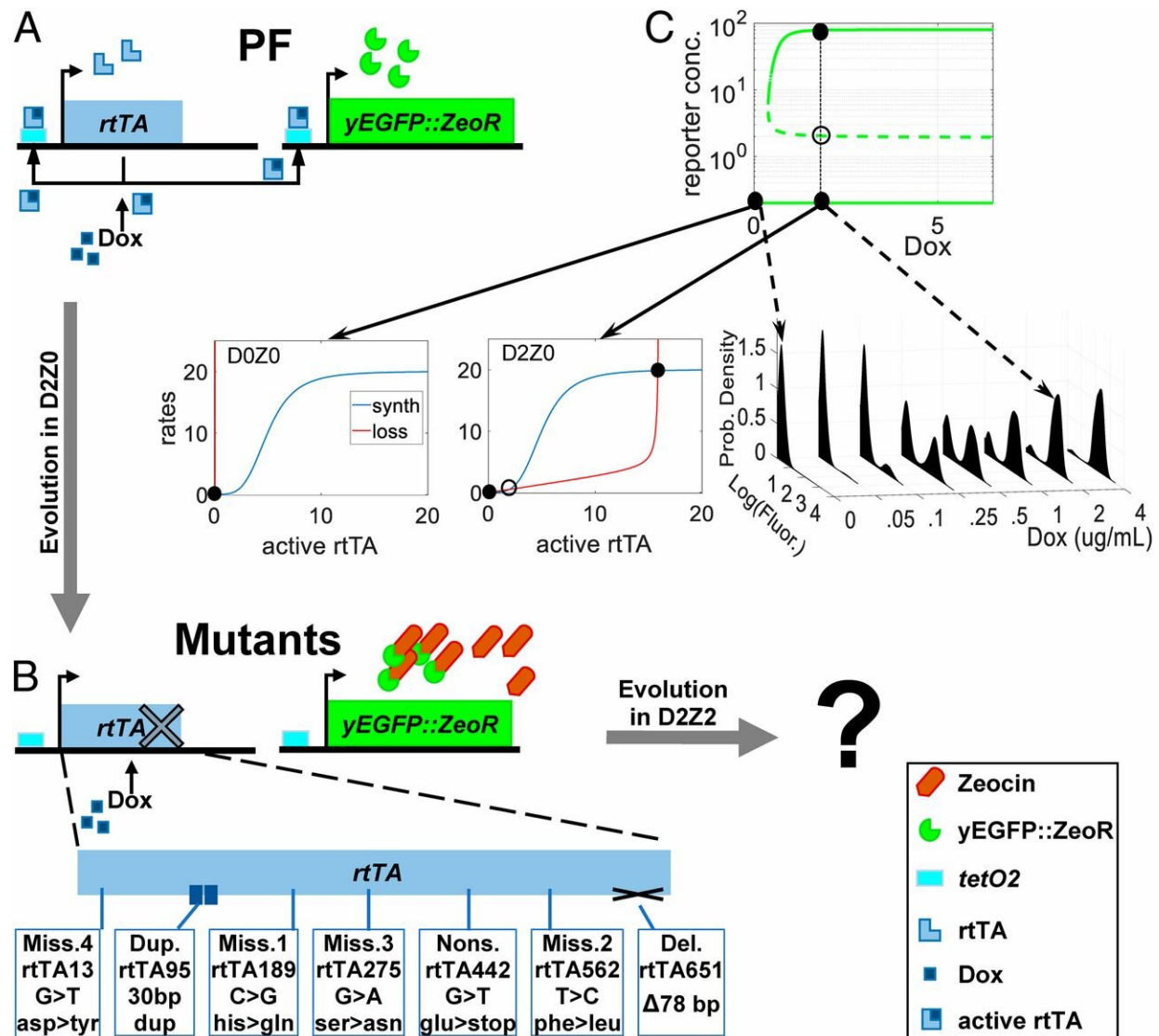


Study shows evolution turns genes back on to regain function

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The PF gene circuit lost bistability and costly *rtTA* function by multiple mutations. (A) In the original PF gene circuit, the inducer Dox binds and

activates the rtTA protein, which identically activates its own rtTA gene and yEGFP::zeoR. Since rtTA activity is costly, loss of rtTA function is evolutionarily beneficial in D2Z0. (B) We selected 7 mutants that arose in D2Z0, each improving fitness by PF breakdown. Now we evolve each mutant in D2Z2 where regaining rtTA function would be beneficial. DxZy denotes the concentrations of the inducer Dox and the antibiotic Zeocin in micrograms per milliliter and milligrams per milliliter, respectively. (C) The original PF gene circuit undergoes a saddle-node bifurcation, changing from monostable to bistable dynamics when Dox exceeds a threshold. The top graph shows yEGFP::zeoR levels versus Dox from a simple mathematical model (SI Appendix, Mathematical Modeling). The blue and red curves on the bottom graphs represent inactive rtTA synthesis and loss rates; while filled and open circles denote stable and unstable steady states, respectively. The active rtTA levels corresponding to the circles impose the yEGFP::zeoR levels on the top graph and on the right, where experimental yEGFP::zeoR expression histograms versus Dox demonstrate the bifurcation. Credit: *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1912257116

Genes often mutate and lose their natural or synthetic function over long-term evolution, which could be good if that stops drug resistance of infectious microbes or cancer. A new study by Stony Brook University researchers, published online in *PNAS*, shows that evolution can exploit positive feedback (PF) within cells to restore gene function. Such repair by evolution may provide a basis for regaining lost gene function, which has implications in medicine and other scientific endeavors.

Based on the idea and experiments of an undergraduate Biomedical Engineering student, Mirna Kheir, and led by Gábor Balázsi, Ph.D., the Henry Laufer Associate Professor in Stony Brook University's Laufer Center for Physical and Quantitative Biology, and Department of Biomedical Engineering, the study included using synthetic PF in [yeast cells](#) by way of a chromosomally integrated gene circuit to test the process of regaining lost gene functions.

"We showed through these experiments and computational models that many drugs can activate mutant resistance genes through this process," explains Balázsi. "Essentially we exposed mutant, drug-sensitive cell populations to conditions where regaining resistance would be beneficial, and we found adaptation scenarios with or without repairing lost gene circuit function."

The results also suggest that inactive, nonfunctional natural drug resistance modules can also regain function upon drug treatment, quickly converting drug-sensitive cancer cells or microbes in drug-resistant ones.

More information: Mirna Kheir Gouda et al. Evolutionary regain of lost gene circuit function, *Proceedings of the National Academy of Sciences* (2019). [DOI: 10.1073/pnas.1912257116](https://doi.org/10.1073/pnas.1912257116)

Provided by Stony Brook University

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