Negative feedback loops help maintain the function of mutated proteins

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Negative feedback is a universal control mechanism that lets a system's output throttle its input. If an engine revs up, negative feedback tapers its power source. But if the engine slows down, it re-opens the power source, keeping output reliably steady. This is an example of a negative feedback that can be found in many systems. In biology, for example, genes under negative regulatory feedback increase (or decrease) their expression in response to falling (or rising) concentrations of the gene product.

Remarkably, for such a well-known control system, a new report that unites mathematics with gene regulation experiments demonstrates a new role for negative feedback: it acts as a shock absorber to buffer the damage of mutations. As a result, genes under negative self-regulatory feedback are freer to mutate, possibly feeding into a wellspring for evolution.

The work appears in *Physical Review Letters*. "This study pins down a process by which some mutations may foster an organism's long term adaptation while putting its immediate fitness at less risk. It is gratifying to see how math and biology come together to suggest a new mechanism relevant for evolution," says Cullen Chair and Professor Olivier Lichtarge, in whose laboratory the work was done, in collaboration with Associate Professor Christophe Herman, both colleagues in molecular and human genetics at Baylor College of Medicine, in Houston.

The study lead authors, Drs. David Marciano and Rhonald Lua, also at

Baylor, followed up on their previous and unexpected observation of mutational tolerance in the bacterial LexA gene (*Cell Reports*, 2014). Here, Lua first built a set of equations that predicted the behavior of a negative regulatory feedback loop and Marciano then compared its predictions to experimental results as each of its components was successively altered. As modeled, they found that mutational tolerance and feedback sensitivity are largely coupled. A gene circuit that strongly responds to perturbations maintains the function of a mutated protein product better than a less responsive gene circuit. This was verified over several biological gene circuits in *E. coli*, at one point engineering one that maintained function despite normally overwhelmingly disabling gene mutations.

"This is of particular importance," noted Marciano, "because mutations deliver the heritable variation upon which natural selection acts. This suggests the ability of gene networks to reshape the mutational landscape of a protein could significantly influence the course of evolution."

The new role of negative feedback loops can also be applied to the field of cancer biology. There are many proteins involved in cancer, such as p53, whose expression is regulated by negative feedback loops. "Defects in negative feedback mechanisms can enhance signals that promote tumorigenesis," said Marciano. "Disruption of p53's negative feedback loops results in cancer cells becoming extremely sensitive to radiation. Multiple clinical trials are underway to target p53 or its feedback loop."

More information: Cooperativity of Negative Autoregulation Confers Increased Mutational Robustness, *Phys. Rev. Lett.* 116, 258104 – Published 22 June 2016 dx.doi.org/10.1103/PhysRevLett.116.258104

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