

Beyond a 'speed limit' on mutations, species risk extinction

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Harvard University scientists have identified a virtual "speed limit" on the rate of molecular evolution in organisms, and the magic number appears to be 6 mutations per genome per generation -- a level beyond which species run the strong risk of extinction as their genomes lose stability.

By modeling the stability of proteins required for an organism's survival, Eugene Shakhnovich and his colleagues have discovered this essential thermodynamic limit on a species's rate of evolution. Their discovery, published this week in the *Proceedings of the National Academy of Sciences*, draws a crucial connection between the physical properties of genetic material and the survival fitness of an entire organism.

"While mathematical genetics research has brought about some remarkable discoveries over the years, these approaches always failed to connect the dots between the reproductive fitness of organisms and the molecular properties of the proteins encoded by their genomes," says Shakhnovich, professor of chemistry and chemical biology in Harvard's Faculty of Arts and Sciences. "We've made an important step toward finally bridging the gap between macroscopic and microscopic biology."

According to Shakhnovich, crucial aspects of an organism's evolutionary fitness can be directly inferred by inspecting its DNA sequences and analyzing how the proteins encoded by those sequences fold. DNA sequences encode the order of amino acids in a protein, and amino acids act as the protein's basic building blocks by arranging themselves into a

structure that allows the protein to perform its biological function.

The research was inspired in part by the longstanding recognition that knocking out essential genes, making them inactive, produces a lethal phenotype, or a physiologically unviable organism.

"From there, we made the simple assumption that in order for an organism to be viable, all of its essential genes -- those that support basic cell operations -- have to encode at least minimally stable proteins," says Shakhnovich. "What occurs over the long process of evolution is that random mutations can either encode slightly more or less stable proteins."

If enough mutations push an essential protein towards an unstable, non-functional structure, the organism will die. Shakhnovich's group found that for most organisms, including viruses and bacteria, an organism's rate of genome mutation must stay below 6 mutations per genome per generation to prevent the accumulation of too many potentially lethal changes in genetic material.

The existence of a mutation limit for viruses helps explain how the immune system can perform its function. Because viral replication and survival can only occur at a limited rate, the body has a window of time to develop antibodies against infectious agents. Furthermore, if the mutation rate is high, the size of the genome in question must be small to stay within the bounds of the speed limit -- thus organisms that tend to mutate quickly are those with concise genomes, such as viruses and bacteria.

The Shakhnovich speed limit also offers an explanation for observed differences in genome sizes between organisms with genome error correction -- such as bacteria, mammals, birds, and reptiles -- and those without, such as RNA viruses: In more complex organisms, cells have

evolved correction systems to detect and fix errors in DNA replication. These systems drastically reduce the number of mutations per replication, increasing the mutational stability of the genome and allowing more intricate and delicate biological systems to develop without the risk of interruptive mutations.

"It's an interesting corollary because it suggests that there is a fundamental tradeoff between evolutionary security and adaptive flexibility: Larger, more complex organisms have to have error correction to protect organismic viability, but this means the rate of evolution slows down significantly," Shakhnovich says. "As organisms become more complex, they have more to lose and can't be as radically experimental with their genomes as some viruses and bacteria."

Source: Harvard University

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