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The Wild Side
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Evolving Mistakes

Being the second part of [an occasional series](#) looking at mutations.

As I mentioned in the first installment of this series, mutations are the raw material for evolution, the ultimate source of innovation: without them, eyes could not get keener, nor feathers snazzier. Yet mutations are also a product of evolution. Which is to say, the rate at which you have mutations is a trait like any other — height, bushiness of eyebrows, number of tentacles and so on — and like any other trait, it can, and does, evolve.

Unlike most other traits, however, mutation rates have a direct effect on evolutionary potential. Understanding how mutation rates evolve thus gives an insight into the evolution of novelty. Nor is this just of academic interest: evolving mutation rates play an important role in the biology of some infectious diseases. So this week I want to consider some of the forces that shape mutation rates themselves.

To recap: mutations are accidental changes to an organism's DNA. They can happen for a number of reasons, but one of the most important is when the cellular machinery makes a mistake as it copies DNA from one cell to the next. The incidence of mutations, then, is affected by how good the machinery of the cell is at copying DNA. High fidelity copying means a low mutation rate; low fidelity means lots of mutations.

Mutations can happen whenever DNA is copied — whether you're making new skin or heart cells, or eggs and sperm. But from an evolutionary point of view, the mutations that matter are the ones that appear in a genome from one generation to the next.

At the physical level of DNA, there are many different kinds of mutations. The ones whose incidence is easiest to measure, and that I'm mainly talking about in this article, are "point mutations" and "indels" (or as I like to think of them, "infidels"). A point mutation is where one element in the DNA sequence is substituted for another, leaving the sequence the same length as it was before. Indel stands for "insertion or deletion"; here bits of sequence are added in or chopped out, usually as a result of the copying machinery slipping and losing its place.

The most obvious way for mutation rates to evolve is through changes — mutations — to the genes that affect how well DNA gets copied. And there are big differences in fidelity. The DNA copying machinery of the bread mold *Neurospora crassa* is about 10 times more accurate than that of the gut bacterium *E. coli*, for example. Intriguingly, however, both organisms end up with about the same number of mutations each time their genomes are copied, because the genome of *Neurospora* is about 10 times bigger.

Most of the time, if a mutation has a detectable effect it will be a bad one, leading to disruption

of a process that's working. This is because mutations are largely random. If you randomly changed some of the letters in this sentence, you'd most likely get rubbish. Only once in a while would you produce a meaningful word — let alone an improvement.

A colorized electron micrograph of a cluster of *E. coli* bacteria. (Credit: Eric Erbe/Colorization by Christopher Pooley/U.S. Department of Agriculture/Reuters)

So it is with mutations and DNA. In a pair of studies on *E. coli*, for instance, deleterious mutations were found to be 100,000 times more frequent than beneficial ones. Also, while many mutations are unequivocally harmful — they kill you — few are unequivocally helpful. The usefulness of a (non-lethal) change typically depends on circumstance. If you're an *E. coli*, a mutation that confers the ability to digest a particular sugar may be essential if that sugar is the main source of available fuel, but irrelevant in an environment where the sugar is lacking.

The observation that most visible mutations are harmful led the great geneticist Alfred Sturtevant to argue in 1937 that mutation rates should evolve to be as close to zero as possible. (Reaching zero is impossible, and anyway, after a point, the time and energy required to drive the mutation rate below a certain threshold will be so great that it's cheaper to have a few mutant offspring. In general, the more accurately the cell copies DNA, the more slowly it does so; and for many organisms, copying DNA too slowly is a disadvantage.)

For organisms such as humans, banana slugs or great white sharks, that regularly engage in sexual reproduction, Sturtevant is probably right: lower mutation rates are better. The reason is that for these organisms, mutations aren't necessary as an immediate source of genetic novelty. Sex does the job instead, shuffling genes and generating children that are genetically different from their parents.

But for some beings, mutations are the main immediate source of genetic novelty. This is where things get interesting.

The mutation rate champions are a group of viruses that include poliovirus and influenza A. These troublemakers don't use DNA to store their genetic information; instead, they use a related molecule, RNA. Their mutation rate is so high that, were it much higher, the viruses would go extinct, because all their progeny would carry lethal mutations. As it is, a high proportion of the progeny carry mutations that render them weak or dead.

A virus like poliovirus can bear a high death rate because each virus particle can quickly give rise to huge numbers — we're talking tens of thousands, or even millions — of descendants. If half of 10 million descendants die, you're still left with 5 million that are viable; of these, some will have beneficial mutations. Moreover, the survival of these viruses depends on their being able to change rapidly, in order to keep dodging the host's immune system. When the mutation rate is lower — and from time to time, mutants appear that do have a lower mutation rate — the virus is more likely to be rounded up and destroyed.

Because their mutation rate is so close to the edge of the possible, one approach to treating infections caused by these viruses is "lethal mutagenesis." The idea is that if you can increase the viral mutation rate, you can force the viruses into a realm where all their progeny carry harmful mutations, and either die quickly or cannot reproduce.

Like viruses, many bacteria also depend on mutations for the rapid generation of genetic novelty. In comfortable, constant environments — say, a warm nutritious broth in a laboratory — a high mutation rate is a disadvantage. But when the going gets tough, mutators begin to thrive.

A mutator bacterium is one that has a mutation that disrupts part of the DNA copying apparatus. As a result, the fidelity of copying collapses, and the mutation rate skyrockets. In extreme cases — the so-called strong mutators — certain types of point mutation become 100 times more likely, while the incidence of small indels increases by a factor of 1,000.

Mutators generate many harmful mutations in their progeny, but they also generate far more beneficial ones than a regular Joe bacterium: because their mutation rate is high, they have a higher incidence of the rare but good mutations. So in circumstances where rapid genetic innovation is needed — such as famine, or an assault by viruses, or antibiotics, or the mammalian immune system — mutators have an advantage, and begin to spread. Mutators play an important role in some human diseases, for they accelerate the evolution of antibiotic resistance.

Mutators spread because they hitch-hike with the beneficial mutations they produce: the beneficial mutations are favored, and so are the mutator genes that caused them. But this alliance can become deadly. If the mutation rate continues to be very high, these bacteria, too, could tip over into a realm of lethal mutagenesis and extinction. And even if matters don't get as bad as that, there will often come a point — if, for example, the environment has stabilized again — where having a high mutation rate becomes a disadvantage. So for the owners of the beneficial mutations to thrive, the mutator gene must eventually get switched off again.

There are a couple of ways this can happen. Another mutation could restore the fidelity of the copying machinery. Or — this is rather clever — the mutator bacterium could acquire a high-fidelity version of the gene from a non-mutator through a process known as horizontal gene transfer. (Horizontal gene transfer is a bacterial equivalent of sex; it's entirely different from the sort of sex we have, not least because it doesn't happen between generations. When bacteria reproduce, they do it asexually, by dividing in two. When they have sex they do not reproduce; instead, they collect a few new genes which they immediately incorporate into their genome, and begin using. It's as though you were to get genes for, say, better teeth halfway through your life. Genes that confer antibiotic resistance are especially notorious for being spread through horizontal gene transfer.)

Genetic analyses of natural populations of *E. coli* suggest that anti-mutator genes have often been acquired through horizontal gene transfer — far more often than the average gene. Which suggests that the history of these bacteria has featured repeated oscillations from high fidelity to infidelity. At least for these critters, alterations to the mutation rate have repeatedly altered the pulse of evolution itself.

NOTES:

When I refer to “DNA copying machinery,” I mean not only the DNA polymerases involved in

copying DNA, but also the various enzymes involved in preventing and repairing errors; mutations to any of these components can alter the mutation rate.

*For per genome mutation rates and copying accuracy in *Neurospora crassa* and *E. coli*, see Table 4 of Drake, J.W., Charlesworth, B., Charlesworth, D., and Crow, J. F. 1998. “Rates of spontaneous mutation.” *Genetics* 148: 1667-1686. This paper also provides an excellent (if technical) general review of mutation rates and how to measure them, as well as a discussion of the trade-off between speed and accuracy.*

*The rate of deleterious versus beneficial mutations in *E. coli* is reviewed in Denamur, E. and Matic, I. 2006. “Evolution of mutation rates in bacteria.” *Molecular Microbiology* 60: 820-827; also see this paper for the rates of mutation in strong mutators (p. 821) and for a discussion of the circumstances that favor their spread.*

*For Sturtevant’s remarks on why mutation rates should tend towards zero, see Sturtevant, A. H., 1937. “Essays on evolution. I. On the effects of selection on mutation rate.” *Quarterly Review of Biology* 12: 464-467. (Note that this paper was written 16 years before the discovery of the structure of DNA.)*

*For high mutation rates in RNA viruses such as poliovirus and influenza A, see Anderson, J. P., Daifuku, R., and Loeb, L. A. 2004. “Viral error catastrophe by mutagenic nucleosides.” *Annual Review of Microbiology* 58: 183-205. For lower mutation rates in poliovirus being linked to worse performance, see Vignuzzi, M., Stone, J. K., Arnold, J. J., Cameron, C. E. and Andino, R. 2006. “Quasispecies diversity determines pathogenesis through cooperative interactions in a viral population.” *Nature* 439: 344-348. For lethal mutagenesis as an approach to curing viral diseases, see Bull, J. J., Sanjuán, R., and Wilke, C. O. 2007. “Theory of lethal mutagenesis for viruses.” *Journal of Virology* 81: 2930-2939.*

*For the potentially lethal alliance between beneficial mutations and mutator genes, see Gerrish, P. J., Colato, A., Perelson, A. S., and Sniegowski, P. D. 2007. “Complete genetic linkage can subvert natural selection.” *Proceedings of the National Academy of Sciences* 104: 6266-6271. For high mutation rates in bacteria in response to the presence of viruses, see Pal, C., Maciá M. D., Oliver, A., Schachar, I., and Buckling, A. 2007. “Coevolution with viruses drives the evolution of bacterial mutation rates.” *Nature* 450: 1079-1081. For horizontal gene transfer of antimutator genes in *E. coli* see Denamur, E. et al 2000. “Evolutionary implications of the frequent horizontal transfer of mismatch repair genes.” *Cell* 103: 711-721.*

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