

## A Random Analysis

This week I want to indulge my fetish for mutations by addressing a question that a number of readers have asked: Are mutations really random?



Computer generated model of a conformation of DNA. (Credit: Kenneth Eward/Photo Researchers)

To recap: mutations are accidental changes to DNA; they typically happen when DNA is being copied. In terms of their physical impact on DNA, mutations come in a variety of types. Some are small, such as when a short segment of DNA gets accidentally deleted. Some are medium — the duplication of a gene or two. Still others are colossal, as when the whole genome gets duplicated. (There's not necessarily a relationship between the physical size of the mutation and its impact on the organism: a short deletion to a crucial gene can kill you; doubling the genome may — for some plants, at least — have no obvious effect.)

Mutations are random in the same sense that a throw of dice is: there's nothing fixed about what will come up next. In other words, mutations are not determined, or pre-ordained.

But random does not mean that all mutations are equally likely. In a game of poker, after all, the deal is random (or should be!), yet you've got a far better chance of being dealt a pair than four-of-a-kind. Similarly, some mutations are much more probable than others.

This matters. Different types of mutations have different evolutionary consequences. For instance, if deletions are more common than insertions — as they are in fruit flies — genomes may evolve to be small and compact. This can have an impact on other aspects of the organism's physiology. As I mentioned a couple of weeks ago, small genomes are easy to copy quickly, which means cells can divide fast — which means creatures with small genomes often have high metabolisms and fast growth. In contrast, the duplication of a genome potentially allows duplicate copies of some genes to evolve new functions, thus expanding the genetic repertoire of the organism. Indeed, an early ancestor of all of us animals with backbones is thought to have experienced at least one, perhaps two, genome duplications, allowing for an explosion of diversity in complexity and form. So understanding the mutational spectrum — which mutations are more likely and why — is essential for estimating the odds of particular evolutionary trajectories.

But it's not simply a question of writing down all the possible types of mutations and then working out how often they happen. The mutant spectrum varies from one species to the next. In humans, for example, one of the most common types of mutation is the insertion or deletion of a small DNA sequence with a repeating motif, such as ATATAT or AGCAGCAGC. (The letters are shorthand for the bits of DNA known as bases. If you think of the double helix as a spiral staircase, the bases are the small, flat molecules that form the steps. In DNA, there are four bases, adenine, guanine, cytosine and thymine.) Such mutations are implicated in a number of human diseases, including severe diseases of neurological decay such as Huntington's.

The reason mutations to repeated sequences are so common is that, in such repeats, it's easy for the DNA copying machinery of the cell to slip and lose its place, and then put in too many repeats, or too few. (Even for a person, copying something like AAAAAAAAA is harder than copying ACTGTCAG. Ahhh!) And although, obviously, these mutations can only happen in part of the genome where there is a repeated sequence, they happen at such a high rate that each of us probably carries as many new slippage mutations as "point mutations" — mutations that swap one base for another, say A for C.

Even so, not all species are equally prone to slipping up. In the social amoeba

amoeba

*Dictyostelium discoideum*, for example, slippage mutations are about 1000 times less common than they are in humans. This is not because social amoebae don't have many repeated stretches of DNA; on the contrary. Stretches of repeated sequence make up 11 percent of the social amoeba genome — more than is known for any other organism. Instead, the machinery of these cells seems to have evolved a way of copying repeats without making so many mistakes. (What makes an amoeba social? In this case, starvation. In times of abundant food, a *Dictyostelium* amoeba oozes through the soil in solitary splendor, tracking, capturing and eating bacteria. But when food runs out, amoebae come together and form an entity known as the slug. The slug creeps off until it finds suitable conditions, then turns into a fruiting body, which releases new amoebae.)

Nor is it just that different types of mutations happen at different rates in different organisms. Complicating matters further, mutations of a given type are not equally likely to happen in all parts of the genome: genomes have mutational hotspots (where mutations are likely) and coldspots (where they're not). Mutations to repeated segments of DNA, for example, are more likely to happen in a repeat that is already long — say 20 iterations of the motif — than in one that is short (2 or 3 iterations). The reason is simple: copying a long repeated segment without slipping is more difficult than copying a short one.

Some bacteria have evolved to exploit this. *Haemophilus influenzae* and *Neisseria meningitidis* — both of which are human pathogens — have evolved repeated sequences in genes that are important for infiltrating host defenses, making these genes prone to mutation. (Although mutations are, in general, bad for an organism more often than they are useful, there can be exceptions. Mutations that allow a pathogen to suddenly change its external appearance can be essential for eluding capture by the host's immune system, for example.) And because the repeats are local to genes involved in pathogenesis, the mutations don't disrupt other genes — such as those important in general maintenance and repair.

A final wrinkle. The bread mold *Neurospora crassa* has evolved an unusual kind of mutational hotspot. Whenever a large segment of DNA gets duplicated—here we're not talking about the short repeated motifs I've been talking about so far, but a chunky sequence, perhaps several hundred bases long — the cellular machinery peppers both the new copy and the original with point mutations. This has the effect of turning both copies into nonsense. (The process is called RIP, for repeat-induced point mutation; it happens during sex.)

This peculiar phenomenon seems to have evolved as a way to control parasitic stretches of DNA — bits of DNA that just replicate themselves, sometimes at the expense of the organism. The human genome is stuffed with such sequences. *Neurospora* is not.

But the mutational peppering has a consequence. As I mentioned at the start of this article, an important source of evolutionary novelty is when one member of a pair of duplicated genes evolves to take on a new function. In *Neurospora* this can't happen: duplicated gene pairs get destroyed. Its use of mutations to defend its genome from invasion may have inadvertently blocked off some evolutionary paths.