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NEWS AND COMMENTARY

Mutation rates

When the going gets tough, beneficial mutations get going

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Breed almost any organism under conditions where it is forced to accumulate random mutations, its fitness will invariably decay. The reason is that very few mutations improve an organism's ability to survive or reproduce; the majority are harmful. But a recent study suggests that the size of this majority depends, to a surprising extent, on the contact in which the mutations occur. The same mutation occurring in a poorly adapted individual, Silander *et al*. (2007) argue, is more likely to be beneficial than if it occurred in a well-adapted individual.

These results are noteworthy because they suggest that the effects of mutations are dynamic rather than fixed. Such a view is consistent with some models of evolution and not with others. For example, it suggests that very small populations, which tend to accumulate harmful mutations, will be protected from the endless accumulation of more and more harmful mutations by an increasing rate of beneficial mutation. This 'compensatory mutation' view contrasts with the 'mutational meltdown' view, which instead suggests that such populations will suffer a build-up of harmful mutations until they become extinct (Poon and Otto, 2000). The findings may have implications for models of adaptive evolution as well; they suggest that after some period of improvement, finite populations may simply run out of new ways to tweak their fitness to ever higher levels (Hartl and Taubes, 1998).

To investigate this, Silander *et al*. (2007) applied techniques first used decades ago to study the fitness effects of mutations in *Drosophila* (Mukai, 1964), but instead used a virus system, a DNA bacteriophage known as ΦX174. With the addition of sophisticated statistical tools and computer simulations, they were able to estimate the proportion of beneficial mutations in virus lines with both high and low fitness. For all three high-fitness lines measured, they were unable to detect any beneficial mutations. But for two out of three low-fitness lines, beneficial mutations were clearly evident. In fact, the fraction of mutations inferred to be beneficial was substantial—16%.

Silander *et al*. (2007) reasoned that the combination of a high rate of beneficial mutations and low fitness, or a low beneficial rate and high fitness, might compensate for one another in the long run. The result would be populations that evolve toward an unchanging, equilibrium fitness. To investigate this possibility, they propagated virus populations in the laboratory, under conditions that allow mutations to accumulate. As expected, the fitness of well-adapted viruses declined precipitously, similar to what has been found in many other studies. But, as Silander *et al*.'s (2007) findings predict, some low-fitness viruses were able to maintain, or even improve, their fitness. In other words, populations did appear to be converging on an equilibrium fitness value. In addition, when virus populations were instead propagated under conditions that allow adaptive evolution, their fitness improved at first and then reached a stable value. Again, the populations evolved toward an equilibrium fitness value. Remarkably, Silander *et al*. (2007) were able to use their estimate of the beneficial mutation rate to predict, with reasonable accuracy, the value of the fitness equilibria.

This work is not without its challenges. For example, it is very difficult to eliminate alternative explanations for fitness equilibria. One possibility is that low-fitness populations, which suffer from more deleterious mutations, could simply be experiencing a high rate of back mutation—that is, the fitness decline might halt simply because the harmful mutations are changing back to the more benign versions of themselves. Silander *et al*. (2007) approached this problem by using a mutagen to ensure that nearly all of the mutations in their study were in one direction (from a cytosine nucleotide to a thymine). Another possibility is that selection is working overtime in low-fitness populations, helping them to maintain their fitness: a mutation might well be more harmful in an already sick virus than it is in a healthy individual. Since the worst mutations are quickly eliminated—dead viruses do not replicate—selection would, in this case, more effectively curtail further fitness decline in low-fitness populations. But, as Silander *et al*. (2007) show, selection is acting only slightly more strongly in low-fitness populations, and the difference is not large enough to explain their results. Finally, since these experiments are inherently difficult and high numbers of replicates hard to achieve, the estimates of the beneficial mutation rate come from only a few samples of high- and low-fitness viruses. As a result, the rates for high- and low-fitness phage are not precisely estimated, and the confidence intervals of the estimates show a broad range of overlap.

However, even if the differences between high- and low-fitness populations are real, it may be that what is true for viruses may not hold for other organisms. Other work, including some that use direct measurements of the fitness effects of known mutations, has suggested that mutations might behave differently in viruses than they do in more complex organisms (Sanjuan and Elena, 2006). Nevertheless, the results from this study are consistent with what has been found in some studies of more complex organisms (Estes and Lynch, 2003). Furthermore, the use of viruses for this kind of work opens up exciting future possibilities. Viral genomes are small and easily manipulated, and viral fitness is straightforward to measure. Thus, the main result of Silander *et al*. (2007), that particular mutations have different effects in high- versus low-fitness virus lines, could potentially be tested directly.

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