

Evolution is unpredictable and irreversible, biologists show

June 8 2015

Evolutionary theorist Stephen Jay Gould is famous for describing the evolution of humans and other conscious beings as a chance accident of history. If we could go back millions of years and "run the tape of life again," he mused, evolution would follow a different path.

A study by University of Pennsylvania biologists now provides evidence Gould was correct, at the [molecular level](#): Evolution is both unpredictable and irreversible. Using simulations of an evolving protein, they show that the [genetic mutations](#) that are accepted by [evolution](#) are typically dependent on [mutations](#) that came before, and the mutations that are accepted become increasingly difficult to reverse as time goes on.

The research team consisted of postdoctoral researchers and co-lead authors Premal Shah and David M. McCandlish and professor Joshua B. Plotkin, all from Penn's Department of Biology in the School of Arts & Sciences. They reported their findings in this week's Early Edition of the *Proceedings of the National Academy of Sciences*.

The study focuses exclusively on the type of evolution known as purifying selection, which favors mutations that have no or only a small effect in a fixed environment. This is in contrast to adaptation, in which mutations are selected if they increase an organism's fitness in a new environment. Purifying selection is by far the more common type of selection.

"It's the simplest, most boring type of evolution you can imagine," Plotkin said. "Purifying selection is just asking an organism to do what it's doing and keep doing it well."

As an evolutionary model, the Penn team used the bacterial protein argT, for which the three-dimensional structure is known. Its small size means that the researchers could reliably predict how a given genetic mutation would affect the protein's stability.

Using a computational model, they simulated the protein evolving during the equivalent of roughly 10 million years by randomly introducing mutations, accepting them if they did not significantly affect the protein's stability and rejecting them if they did. They then examined pairs of mutations, asking whether the later mutation would have been accepted had the earlier mutation not have been made.

"The very same mutations that were accepted by evolution when they were proposed, had they been proposed at a much earlier in time, they would have been deleterious and would have been rejected," Plotkin said.

This result—that later mutations were dependent on the earlier ones—demonstrates a feature known as contingency. In other words, mutations that are accepted by evolution are contingent upon previous mutations to ameliorate their effects.

The researchers then asked a distinct, converse question: whether it is possible to revert an earlier mutation and still maintain the protein's stability. They found that the answer was no. Mutations became "entrenched" and increasingly difficult to revert as time went on without having a destabilizing effect on the protein.

"At each point in time, if you make a substitution, you wouldn't see a

large change in stabilization," Shah said. "But, after a certain number of changes to the protein, if you go back and try to revert the earlier change, the protein structure begins to collapse."

The concepts of contingency and entrenchment were well known to be present in adaptive evolution, but it came as a surprise to the researchers to find them under purifying selection.

"We thought we would just try this with purifying selection and see what happened and were surprised to see how much contingency and entrenchment occurs," Plotkin said. "What this tells us is that, in a deep sense, evolution is unpredictable and in some sense irreversible because of interactions between mutations."

Such interactions, when the effect of a mutation is dependent on another, are known as epistasis. The researchers' investigation found that, unexpectedly, purifying selection enriches for epistatic mutations as opposed to mutations that are simply additive. Plotkin explained that this is because purifying selection favors mutations that have a small effect. Either the mutation can have a small effect on its own, or it can have a small effect because another, earlier mutation ameliorated the effects of the current mutation. Thus mutations that are dependent upon earlier mutations will be favored.

"Our study shows, and this has been known for a long time, that most of the substitutions that occur are substitutions that have small effects," McCandlish said. "But what's interesting is that we find that the substitutions that have small effects change over time."

An implication of these findings is that predicting the course of evolution, as one might wish to do, say, to make an educated guess as to what flu strain might arise in a given year, is not easy.

"The way these substitutions occur, since they're highly contingent on what happened before, makes predictions of long-term evolution extremely difficult," Plotkin said.

The researchers hope to partner with other groups in the future to conduct laboratory experiments with microbes to confirm that real-world evolution supports their findings.

And while Gould's comment about replaying the tape of life was mainly a nod to the large amount of randomness inherent in evolution's path, this study suggests a more nuanced reason that the playback would appear different.

"There is intrinsically a huge amount of contingency in evolution," Plotkin said. "Whatever mutations happen to come first set the stage for what other later mutations are permissible. Indeed, history channels evolution down a certain path. Gould's famous tape of life would be very different if replayed, even more different than Gould might have imagined."

More information: Contingency and entrenchment in protein evolution under purifying selection, *PNAS*,
www.pnas.org/cgi/doi/10.1073/pnas.1412933112

Provided by University of Pennsylvania

Citation: Evolution is unpredictable and irreversible, biologists show (2015, June 8) retrieved 3 May 2024 from <https://phys.org/news/2015-06-evolution-unpredictable-irreversible-biologists.html>

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