Mutation accessibility fuels influenza evolution

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The influenza (flu) virus is constantly undergoing a process of evolution and adaptation through acquiring new mutations. Scientists at St. Jude

Children's Research Hospital have added a new layer of understanding to explain why and how flu viruses change. The "survival of the accessible" model provides a complementary view to the more widely recognized "survival of the fittest" way of evolving. The work was published today in *Science Advances*.

Viruses undergo a rapid evolutionary flux due to constant genetic mutations. This rapid flux is why people get a flu shot every year, as we need to tackle the latest flu variant that has emerged as the dominant strain. We often see these mutations in the context of traditional evolutionary thinking, where variant fitness determines which mutated virus emerges as a dominant strain in a population. The St. Jude team investigated this theory and defined an alternative evolutionary principle, which they propose is a key driver of evolution, termed "variant accessibility."

The research, led by Alexander Gunnarsson, Ph.D., and M. Madan Babu, Ph.D., St. Jude Department of Structural Biology and Center of Excellence for Data-Driven Discovery, involved creating a model of mutational accessibility to help predict how and why specific mutations emerge in a population during viral evolution.

The unappreciated role of variant accessibility

The genomic alphabet only has four letters representing the nucleotides: (A)denosine, (T)hymine, (G)uanine, and (C)ytosine. Groups of three nucleotides within a protein-coding gene are called a codon. Codons act like a recipe for assembling proteins, encoding for a specific amino acid. Mutations occur when nucleotides are altered, for instance, during replication. This alteration leads to a different amino acid being used to make the protein. But not all mutations are equally likely to emerge, as Babu and Gunnarsson discovered.

"The process of genetic replication has inherent biases built in, such as the relative ease of an A to be mutated to a C rather than to a G," Babu explained. "This means that the pool of mutants with this A-to-C mutation is larger, and surviving variants will predominantly emerge from that particular pool, even though there may be a fitter sequence with an A-to-G mutation."

Using the influenza virus as a case study, Gunnarsson and Babu translated this concept into a mathematical model. Their model enables researchers to predict the path of future evolution based on the accessibility of a mutation. Of particular interest was exploring how specific protein sites can gain or lose the ability to be modified after acquiring a mutation. They then examined how this gain or loss influenced the protein's function.

Phosphorylation is an example of such a modification. It occurs when a phosphate molecule is added to specific amino acids of a protein. In terms of the flu, phosphorylation can help the virus hijack the host molecular pathways for mediating successful infection. Such mutations may have been critical to influenza pandemics of the past, and it is these datasets that Gunnarsson and Babu used to develop their model.

The importance of jackpot events

The model also helped the researchers better understand a long-conceptualized mutation property, the jackpot event. These are mutations that occur by chance early in the growth of a population, leading to a continuous benefit seen throughout the descendants. "The more accessible a genotype is, the more frequent these specific jackpot events are because it's simply a probabilistic event," Gunnarsson explained. "If a particular gene is a hundred times more likely to acquire a specific mutation, you'll see that jackpot event happening proportionately more frequently. These events are important in evolution

and are driven primarily by how accessible the variants are."

More accessible mutations are likely to be predominant in a population even though they may not be the fittest mutation. "If the probability of acquiring the fittest mutation is one out of hundreds of trillions," Gunnarsson said, "the likelihood of it reaching fixation in a population, even if it's the fittest mutation, is low. When you have multiple instances of jackpot mutations happening, statistically, the prevalence of this variant increases massively, even if it's less fit compared to another, more fit but less accessible mutant."

Furthering our understanding of mutational bias and predicting outcomes in evolving systems

The concept of variant accessibility is elegant in its simplicity, but like most things in nature, it is a balance of statistical probabilities. From the mutation event and differences in the probability of certain nucleotide changes to codon redundancy (multiple codons for the same amino acid), it is a delicate balance between components that drives evolutionary pathways.

"Furthering our understanding of biochemical mutational biases (e.g., during replication) in viruses can open up new directions and possibilities because it'll give much better insights into how a virus is likely to evolve," Babu stated. In fact, the model is being applied to historical data about how the flu virus has changed within the framework of mutational accessibility to predict viral evolution more accurately.

The ability to predict viral evolutionary outcomes based on accessibility has piqued the interest of influenza expert Richard Webby, Ph.D., of St. Jude Department of Host-Microbe Interactions and Director of the World Health Organization Collaborating Centre for Studies on the

Ecology of Influenza in Animals and Birds.

"There are many scenarios in public health where we try and predict the evolutionary path of influenza viruses, including selecting the most appropriate vaccines for future influenza," Webby said. "The 'survival of the accessible' model will empower these predictions and allow us to identify viruses more likely to take on worrying traits more confidently."

This model also applies beyond influenza or even virology and steers further research into mutational biases in different diseases. In cancer, for example, the model can help answer numerous questions about pathology, such as why particular cancer-driving or drug-resistance mutations repeatedly surface.

"Our model can be applied to help predict whether a particular type of mutation is likely to emerge as a tumor driver or as a resistant mutation to a specific treatment," Babu stated. "We hope our work will spur research into characterizing mutational biases driving viral and tumor evolution. If we can quantify and better understand the biochemical processes contributing to mutational bias, that will be invaluable to predict mutational outcomes in evolving genetic systems. The ability to predict outcomes before they happen will allow us to be prepared when they eventually unfold."

More information: P. Alexander Gunnarsson et al, Predicting Evolutionary Outcomes Through the Probability of Accessing Sequence Variants, *Science Advances* (2023). DOI: 10.1126/sciadv.ade2903. www.science.org/doi/10.1126/sciadv.ade2903

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