Researchers develop a physical model of the optimal immune repertoire for bacteria

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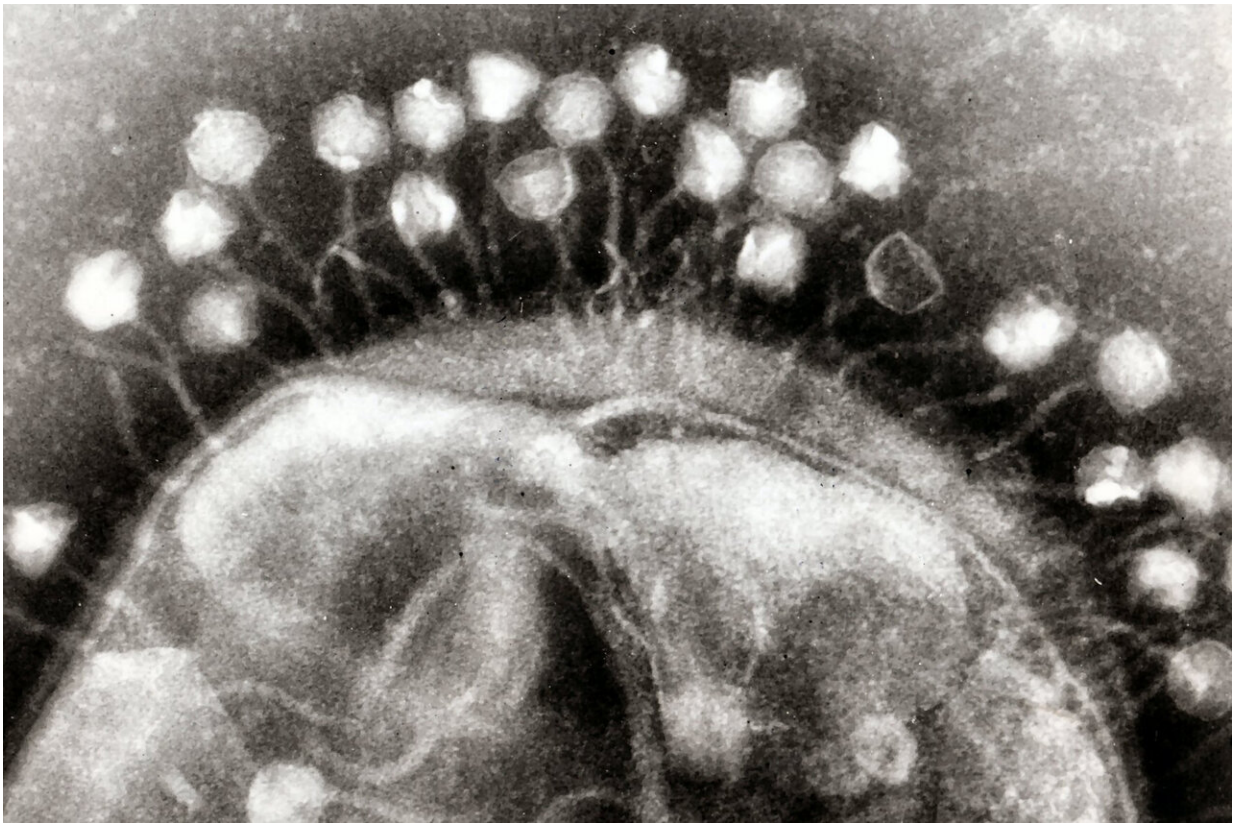

Transmission electron micrograph of multiple bacteriophages, viruses that infect bacteria, attached to a cell wall. New research describes how bacteria can optimize their "memory" of past viral infections in order to launch an effective immune response against a new invader. Credit: Graham Beards

Before CRISPR became a household name as a tool for gene editing,

researchers had been studying this unique family of DNA sequences and its role in the bacterial immune response to viruses. The region of the bacterial genome known as the CRISPR cassette contains pieces of viral genomes, a genomic "memory" of previous infections. But what was surprising to researchers is that rather than storing remnants of every single virus encountered, bacteria only keep a small portion of what they could hold within their relatively large genomes.

Work published in the *Proceedings of the National Academy of Sciences* provides a new physical model that explains this phenomenon as a tradeoff between how much memory bacteria can keep versus how efficiently they can respond to new viral infections. Conducted by researchers at the American Physical Society, Max Planck Institute, University of Pennsylvania, and University of Toronto, the model found an optimal size for a bacteria's immune repertoire and provides fundamental theoretical insights into how CRISPR works.

In recent years, CRISPR has become the go-to biotechnology platform, with the potential to transform medicine and bioengineering. In bacteria, CRISPR is a heritable and adaptive immune system that allows cells to fight viral infections: As bacteria come into contact with viruses, they acquire chunks of viral DNA called spacers that are incorporated into the bacteria's genome. When the bacteria are attacked by a new virus, spacers are copied from the genome and linked onto molecular machines known as Cas proteins. If the attached sequence matches that of the viral invader, the Cas proteins will destroy the virus.

Bacteria have a different type of immune system than vertebrates, explains senior author Vijay Balasubramanian, but studying bacteria is an opportunity for researchers to learn more about the fundamentals of adaptive immunity. "Bacteria are simpler, so if you want to understand the logic of immune systems, the way to do that would be in bacteria," he says. "We may be able to understand the statistical principles of

effective immunity within the broader question of how to organize an immune system."

Because of CRISPR's role in the bacterial immune response, the researchers were interested in developing a physical model that could describe the role of the CRISPR cassette during a viral infection. They were specifically interested in why bacteria tend to store only 50-100 viral DNA snippets, or spacers, from past infections when their genomes could easily hold thousands. "The puzzle is that the bacteria go to the trouble of implementing this memory system, but they keep a shallow memory," says Balasubramanian. "You would think that remembering more would be better."

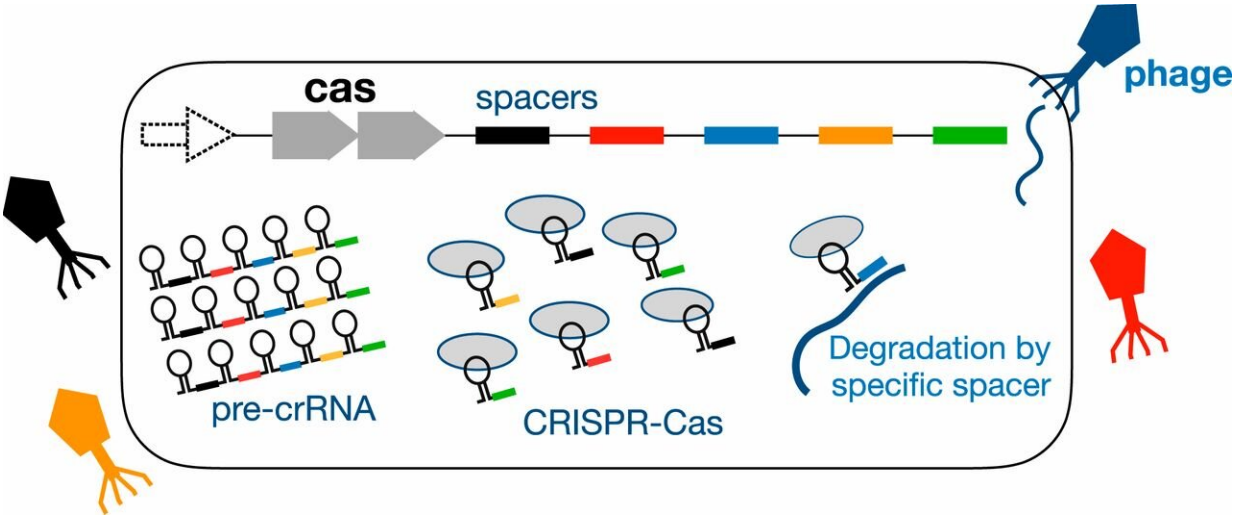

Diagram showing how CRISPR immunity works in bacteria. A bacterium with CRISPR machinery encounters a diverse set of phages, marked by different colors. The CRISPR-Cas locus is transcribed and then processed to bind Cas proteins (gray ovals) with distinct spacers to make CRISPR-Cas complexes. The complex with a spacer that matches the phage DNA is able to attack the virus material and protect the bacterium. Credit: Bradde et al.

As the researchers developed a mathematical model to look at bacterial survival, they could adjust the model's parameters, such as the number of viruses the bacteria encountered and the number of spacers held within the genome, to see how these factors affect the bacteria's overall chance of survival. They found that there was an optimal amount of memory that, surprisingly, only consisted of a few dozen spacers.

Why is having less memory more optimal? "Memory is useless unless you have a way to use it," says Balasubramanian. This is because the spacers must be transcribed and attached onto the Cas proteins that mount an immune response, and there are only so many Cas proteins to go around. This means that there is an opportunity cost to keeping too much memory, which results in a trade-off between how much memory can be stored and how quickly bacteria can respond to a new infection. "Cells are full of molecular machines, and all machines have constraints. Because that machinery is limited, bacteria only keep what's most useful," he says.

Another insight that was a key for their model was the need for multiple Cas protein recognitions of new viral infections. To prevent the bacteria from making mistakes, multiple Cas proteins are required to bind to and recognize a virus before mounting an immune response. By incorporating this requirement into the model, the researchers were able to understand the importance of limited resources, in this case Cas proteins, in determining the optimal amount of bacterial immune memory.

The researchers now plan to look at how other immune mechanisms affect how deep a bacteria's memory should be. They also plan to study how bacteria use their relatively shallow memory to protect themselves from different types of viruses to see if, for example, bacteria keep more memory of viruses that are more dangerous or more common.

This work represents a unique, physics-based approach to study a biological mechanism that has become a widely used tool in biotechnology but still still remains poorly understood in terms of its natural function. "As theorists, we think about the principles underlying function," says Balasubramanian. "This is one of the first papers to try to establish the computational principles underlying CRISPR-based immunity, and it comes to an interesting conclusion."

More information: Serena Bradde et al. The size of the immune repertoire of bacteria, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.1903666117

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