

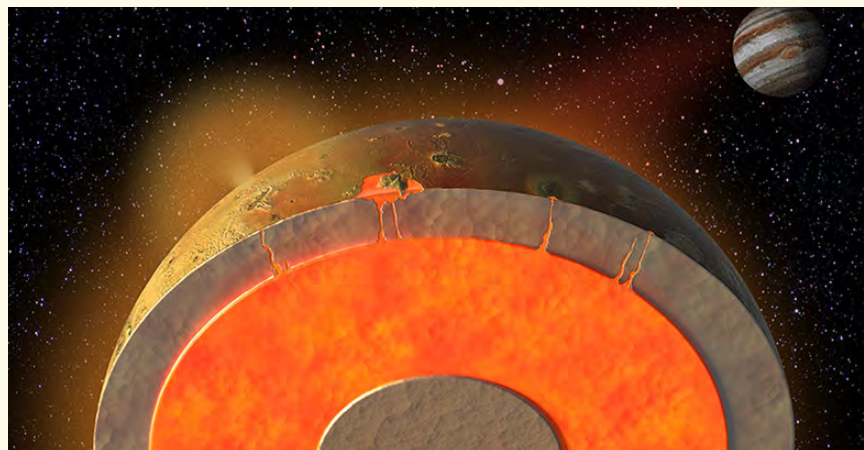
Io was always extremely volcanic, evidence indicates

The Jovian moon's abundance of a heavy sulfur isotope is higher than that of any other object in the solar system.

The most volcanically active object ever observed in the solar system is Io. Its massive and sustained eruptions, extensive lava flows, and huge lava lakes are more substantial than any on Earth and have led researchers to wonder: Has Io always been that way? The question is hard to answer because its surface is constantly changing. In just a million years—which is short by geological standards—Io's entire surface has been repaved by volcanic deposits, destroying craters and other evidence of geologic history over its 4.5-billion-year existence.

Now Katherine de Kleer of Caltech and colleagues have developed a way to study Io's volcanic history by tracking its sulfur. With new isotope evidence and geochemical modeling, they found that Io's volcanism was likely even more pronounced in the past and may have been present over the moon's entire history.

The researchers observed sulfur gases in Io's atmosphere with the Atacama Large Millimeter/Submillimeter Array in Chile. When a gas molecule loses angular momentum, it transitions from a higher rotational energy state to a lower one and, in the process, emits microwave radiation. Each molecule has many unique spectral emission lines that can be ob-



JUPITER'S MOON IO may have experienced large eruptions and lava flows throughout its 4.5-billion-year history. (Image by Chuck Carter and James Tuttle Keane/Keck Institute for Space Studies.)

served. Even molecules made with different isotopes—say, with sulfur-32 and sulfur-34—are distinguishable. With the molecular emission data, the researchers determined the sulfur isotope composition of Io's atmosphere and found that it contains much more ^{34}S than ^{32}S .

In fact, no other measured body in the solar system has such a high ratio of $^{34}\text{S}/^{32}\text{S}$. To interpret Io's unusual sulfur enrichment, one of the paper's coauthors, Ery Hughes, led the development of a geochemical model of Io's interior and its atmosphere. The sulfur ratio likely reflects a geochemical process that begins when sulfur dissolved in magma rises through Io's mantle and erupts from volcanoes. The lighter ^{32}S diffuses into the upper atmosphere more readily than ^{34}S , and then the atmospheric sulfur collides with stray plasma from Jupiter's magnetosphere before being lost to space.

The high $^{34}\text{S}/^{32}\text{S}$ ratio may indicate an especially volcanic past. The geochemical modeling shows that Io could have been losing sulfur in the past at a rate as high as five times what it is today. The extreme volcanism necessary to cause that much sulfur loss comes from tidal heating. Jupiter's intense gravity flexes Io, and the resulting tidal energy dissipates in Io's interior as frictional heat. Io's tidal heating is possible only because of its elliptical orbit around Jupiter, caused by interactions with other Jovian moons. So by learning more about Io's volcanic history, researchers may unravel more about the formation of Jupiter and its moons—and potentially other systems subject to strong tidal forces. (K. de Kleer et al., *Science*, 2024, doi:10.1126/science.adj0625.)

Alex Lopatka

Designer proteins fit like a glove

The bespoke biomolecules interact with molecular targets in predictable, controllable ways.

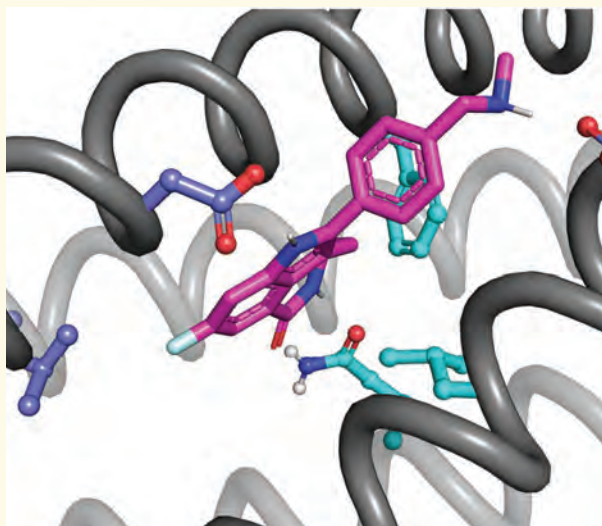
The relationship between protein sequence and structure isn't as much of a mystery as it once was. In late 2020, researchers from DeepMind in London turned heads with their AlphaFold2 model, which uses artificial intelligence to predict

the structures of natural proteins with stunning accuracy. (See *PHYSICS TODAY*, October 2021, page 14.) But there's more to know about a protein than its structure. Proteins aren't static isolated objects—they're constantly interacting with other molecules around them. The energetics and dynamics of those interactions are fundamental to proteins' role as the building blocks of life.

Now researchers led by William DeGrado (University of California, San Francisco), his former postdoc Nicholas Polizzi (now on the faculty at Harvard University), and his current postdoc Lei Lu have unveiled a way to design proteins from scratch so that the proteins not

only bind to a specified target molecule but do so with predictable binding energy. So-called *de novo*-designed proteins, made from amino-acid sequences that nature never exploited, are nothing new. But in most cases, the computed structures need to be experimentally refined with several rounds of mutation and screening before they're fit for purpose. Polizzi and DeGrado's proteins are notable exceptions: At least much of the time, they work on the first try.

The work builds on an underlying approach Polizzi and DeGrado developed several years ago, breaking down the protein-molecule binding problem



STARTING FROM A FEW standard backbone structures, such as the alpha helices shown in gray, protein designers have extraordinary leeway to tune a protein's chemical properties. Here, the amino acid side chains shown in purple and light blue are chosen to bind to a target molecule, shown mostly in pink. (Image adapted from L. Lu et al., *Science* **384**, 106, 2024.)

into pieces called van der Mers. That's not an obscure Dutch surname but rather a portmanteau of "van der Waals" and "rotamer." Rotamers are floppy parts of amino acids; although they can, in principle, adopt enormously many conformations, only a handful of possibilities ever show up in the real proteins in the Protein Data Bank. By limiting themselves to just

the conformations that nature tends to favor, protein designers can radically simplify their computational searches.

As Polizzi and DeGrado discovered, the same strategy works for the van der Waals interaction between amino acids and other molecules: Given an amino acid and the nearest bit of the target molecule, the atoms only ever arrange

themselves in a few discrete ways. By sifting through the ways that the protein-molecule pieces can be packed into a known protein backbone—such as the four-helix structure shown in the figure—the researchers create a *de novo* protein fitted to the target molecule. With judicious choices of amino acids, they can make the binding as strong or as gentle as they like. And they can keep it specific: The protein binds to the target molecule, but not to any others.

The problem the researchers tackled is the inverse of conventional drug design. Given a naturally occurring protein, drug designers want to identify a molecule that binds to it, perhaps to stop it from performing some harmful function in the body. So why design a protein to bind to a given molecule? One possible application is to create antidotes for drugs—to neutralize them and stop their effects. Another is as a first step toward designing artificial enzymes: Before an enzyme can catalyze a reaction, it first needs to bind to the reactant molecule. (L. Lu et al., *Science* **384**, 106, 2024.)

Johanna Miller 

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