the team combined deep learning with an "attention algorithm" that mimics the way a person might assemble a jigsaw puzzle: connecting pieces in clumps—in this case clusters of amino acids—and then searching for ways to join the clumps in a larger whole. Working with a computer network built around 128 machine learning processors, they trained the algorithm on all 170,000 or so known protein structures.

And it worked. In this year's CASP, AlphaFold achieved a median GDT score of 92.4. For the most challenging proteins, AlphaFold scored a median of 87, 25 points above the next best predictions. It even excelled at solving structures of proteins that sit wedged in cell membranes, which are central to many human diseases but notoriously difficult to solve with x-ray crystallography. Venki Ramakrishnan, a structural biologist at the Medical Research Council Laboratory of Molecular Biology, calls the result "a stunning advance on the protein folding problem."

All groups in this year's competition improved, Moult says. But with AlphaFold, Lupas says, "The game has changed." The organizers even worried DeepMind may have cheated somehow. So Lupas set a special challenge: a membrane protein from a species of archaea, an ancient group of microbes. For 10 years, his team had tried to get its x-ray crystal structure. "We couldn't solve it."

But AlphaFold had no trouble. It returned a detailed image of a three-part protein with two helical arms in the middle. The model enabled Lupas and his team to make sense of their x-ray data; within half an hour, they had fit their experimental results to AlphaFold's predicted structure. "It's almost perfect," Lupas says. "They could not possibly have cheated on this. I don't know how they do it."

As a condition of entering CASP, DeepMind—like all groups—agreed to reveal sufficient details about its method for other groups to re-create it. That will be a boon for experimentalists, who will be able to use structure predictions to make sense of opaque x-ray and cryo-EM data. It could also enable drug designers to work out the structure of every protein in new and dangerous pathogens like SARS-CoV-2, a key step in the hunt for molecules to block them, Moult says.

Still, AlphaFold doesn't do everything well. In CASP, it faltered on one protein, an amalgam of 52 small repeating segments, which distort each others' positions as they assemble. Jumper says the team now wants to train AlphaFold to solve such structures, as well as those of complexes of proteins that work together to carry out key functions in the cell.

Even though one grand challenge has fallen, others will undoubtedly emerge. "This isn't the end of something," Thornton says. "It's the beginning of many new things." ■

WATER POLLUTION

Why were salmon dying? The answer washed off the road

Common tire chemical implicated in coho salmon kills

By **Erik Stokstad**

For decades, something in urban streams has been killing coho salmon in the U.S. Pacific Northwest. Even after Seattle began to restore salmon habitat in the 1990s, up to 90% of the adults migrating up certain streams to spawn would suddenly die after rainstorms. Researchers suspected the killer was washing off nearby roads, but couldn't identify it. "This was a serious mystery," says Edward Kolodziej, an environmental engineer at the University of Washington's (UW's) Tacoma and Seattle campuses.

Online this week in *Science*, researchers led by Kolodziej report the primary culprit comes from a chemical widely used to protect tires from ozone, a reactive atmospheric gas. The toxicant, called 6PPD-quinone, leaches out of the particles that tires shed onto pavement. Even small doses killed coho salmon in the lab. "It's a brilliant piece of work," says Miriam Diamond, an environmental chemist at the University of Toronto. "They've done a tremendous job at sleuthing out a very challenging problem."

Particles that erode from tires wash into streams used by coho salmon.

Manufacturers annually produce some 3.1 billion tires worldwide. Tire rubber is a complex mixture of chemicals, and companies closely guard their formulations. Because tire particles are a common component of water pollution, researchers have been examining how they affect aquatic life.

After Kolodziej arrived at UW's Center for Urban Waters in 2014, he joined the effort to solve the coho salmon mystery. The group created a mixture of particles from nine tires—some bought new, others provided by two undergraduates who moonlight as mechanics—to mimic what might wash off typical highways. They found several thousand unidentified chemicals in the mixture. Postdoc Zhenyu Tian spent more than 2 years narrowing down the list, separating the molecules based on their electrical charge and other properties. By May 2019, he had narrowed the focus to about 50 unknown chemicals, and then further work revealed the chemical formula of a prime suspect. "If you're looking for an unexplained toxicant that's killing fish, we had the perfect instruments and expertise," Kolodziej recalls.

But what was it? A 2019 report from the Environmental Protection Agency on chemicals in recycled tires mentioned 6PPD, which has a similar formula. The final clue was buried in an industry report from 1983, which contained the exact formula of 6PPD-quinone, the molecule created when 6PPD reacts with ozone. The team synthesized 6PPD-quinone and found it was highly lethal to coho salmon.

Now, the team is working to understand how the chemical kills fish. Kolodziej and colleagues say other species of fish should also be evaluated for sensitivity. Because you can't buy the molecule, Kolodziej's team is making it. "My lab might even be the only place that actually has this," he says.

The researchers suspect the compound is present on busy roads everywhere. They've found it washes off pavement and into streams in Los Angeles and San Francisco, for example. The simplest solution might be for tire manufacturers to switch to an environmentally benign alternative. But Sarah Amick, vice president of environment, health, safety, and sustainability at the U.S. Tire Manufacturers Association, says it's too early to discuss alternatives. "It's important that additional research be done to validate and verify these results."

Another way to protect salmon is to filter stormwater through soil, but installing enough infiltration basins to treat road runoff before it reaches spawning streams would be very expensive, says co-author Jenifer McIntyre, an ecotoxicologist at Washington State University's Puyallup Research and Extension Center. In the meantime, Kolodziej says he "can't walk along a street without staring at all the skid marks," thinking about tire chemicals, and "wondering what's there." ■

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Science

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