COMPUTATIONAL BIOLOGY

Custom-Built Supercomputer Brings Protein Folding Into View

Scientists have long been frustrated in their efforts to use computers to simulate the atomic detail of how proteins fold into their three-dimensional structures. The computing demands for simulating all the motions of a protein's atoms and the surrounding water are so high that scientists have had difficulty tracking the myriad atomic wiggles and gyrations for long enough to see the complete folding process. But now help is on the way. On page 341, computational biologists led by computer scientist and former hedge fund manager David Shaw report that they ran a specially built supercomputer for about 3 weeks to simulate a relatively small protein going through 15 rounds of folding and unfolding over 200 microseconds. They also tracked the folding gyrations of a similarly sized protein for more than a millisecond.

"This is a landmark paper," says David Baker, a protein-folding expert at the University of Washington, Seattle. Klaus Schulten, a molecular simulations expert at the University of Illinois, Urbana-Champaign, who has been Shaw's friendly rival, agrees, calling the paper "very important."

Baker notes that the simulations from Shaw and his colleagues revealed that the folding protein followed more or less the same general pattern of movements each time it folded rather than each folding having a distinct progression. That was something of a surprise because it wasn't clear from previous modeling and experimental work this would be the case. Others note that simulating individual proteins for long periods isn't the only way to investigate protein folding: networks of computers can also cobble together large numbers of shorter simulations to explore some key events. Still, the new work sets the stage for extended simulations of dozens, if not hundreds, of other proteins that are less well understood, which could reveal whether all proteins follow a similar set of rules as they fold. "Now one can approach these questions in a quantitative manner," Baker says.

That's been Shaw's dream since he left the world of high finance 9 years ago to start an outfit called D. E. Shaw Research in New York City. Shaw, who now also has an affiliation with Columbia University, originally trained as a computer scientist and specialized in designing parallel supercomputers. After a brief stint on the faculty of Columbia in the 1980s, he moved to Wall Street, where he designed powerful algorithms for stock trading. He later moved on to run his own hedge fund, winding up on the Forbes list of 400 richest Americans in the process. (He also recently served as the treasurer of AAAS, *Science*'s publisher.) But Shaw missed the intellectual challenge of science. "I found myself at night solving math problems for fun," he says.

After conversations with friends in computational biology, Shaw chose the challenge of simulating the motion of proteins for his reentry into science. Drawing on his early career, he decided to design and build a customized supercomputer to push the boundaries of the field. Two years ago Shaw revealed the result, Anton, a supercomputer containing 512 specially designed computer chips hard-wired to speed the

CHEMISTRY

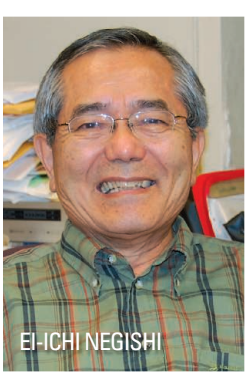
Carbon-Linking Catalysts Get Nobel Nod

Credit the matchmaker for this one. This year's Nobel Prize in chemistry went to three chemists—Ei-ichi Negishi, Akira Suzuki, and Richard Heck—for discovering catalysts used to tie the knot between carbon atoms on separate molecules. The ability to tailor such molecular unions has spawned whole sectors of advanced technology, making possible the synthesis of everything from anticancer drugs and agricultural pesticides to advanced displays and electronic chips in computers.

At the heart of these applications are organic molecules made from chains and rings of carbon atoms. Carbon is the key to organic chemistry—and life—thanks to its ability to link with its neighbors to form molecular chains and rings of an enormous variety of shapes, much as lumber can be nailed together to build houses of almost any design. To build synthetic molecules, chemists continually look for new ways to join together carbon atoms on separate molecules. The trouble is that in most organic molecules, the carbon atoms are happy with where they are and thus unlikely to react with their neighbors. In the early 1900s, German chemists came up with ways to link metal atoms to carbons, making them more reactive and willing to bond with neighbors. But the reactions weren't specific. Instead of producing just the desired molecule, the more-reactive carbons would bond willy-nilly with any carbon around, producing all sorts of junk that had to be tossed out.

CHEMISTRY NOBEL PRIZE 2010

RICHARD HECK



EI-ICHI NEGISHI

AKIRA SUZUKI

In the late 1960s, Heck, then with chemical manufacturing company Hercules Corp. in Wilmington, Delaware, and later at the University of Delaware, Newark, found that he could tailor just which carbons he wanted to link together. In one early example, Heck first linked a bromine atom to one of the six carbon atoms in a molecule of benzene. This slightly modified the electronic structure of the carbon and tagged it as the one that would react. He then added small, two-carbon molecules called olefins to the solution, as well as palladium. The palladium temporarily binds with both the carbon on the bro-

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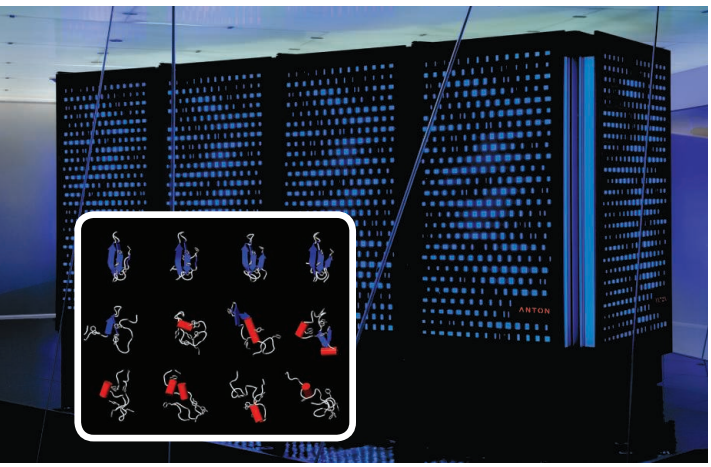

Custom job. By speeding calculations, this Anton supercomputer can run all-atom simulations (*inset*) 100 times longer than can general purpose supercomputers.

relatively simple calculations involved in determining how neighboring atoms in a protein interact. By speeding computations, Shaw says, Anton has run all-atom simulations 100 times longer than general purpose supercomputers can. In the current study, for example, Shaw and his colleagues were able to track 13,564 atoms, comprising a relatively small protein and surrounding water molecules, long enough to see the protein fold and unfold repeatedly.

Like all supercomputers, the Anton used in the current study still has its limits and can't run such lengthy simulations of very large proteins. But Shaw says he and his colleagues are already making progress on that. In addition to building 11 supercomputers incorporating 512 custom-designed computer chip cores, or nodes—Shaw donated one to the National Resource for Biomedical Supercomputing in Pittsburgh, Pennsylvania—Shaw's team has built a 1024-node machine and one with 2048 nodes. The larger machines, he notes, are more efficient tracking the motions of larger proteins. Moreover, Shaw says his team is already building successors to Anton, using the next generation of chip technology to burn through calculations significantly faster. And Shaw says he's happy to be back in the thick of a knotty intellectual challenge: "I love this. It's just the most fun I've ever had. It's very satisfying."

–ROBERT F. SERVICE

mine-tagged benzene as well as one from the olefin, bringing them close enough to pair up. When they do so, they form styrene, the building block of polystyrene plastics. The reacting molecules kick the bromine out into solution and send the palladium on its way to orchestrate another hookup. In the late 1970s, Japanese-born Negishi, who spent the bulk of his career at Purdue University in West Lafayette, Indiana, and Suzuki, of Hokkaido University in Sapporo, Japan, modified the approach, adding different tagging atoms as well as metals to tailor the reaction to make other organic compounds.

Today, the three approaches are collectively known in chemistry parlance as "palladium-catalyzed cross-coupling reactions," and they continue to grow more popular. "Of all methodologies developed over the past 50 years, it is safe to say that palladium-catalyzed cross-coupling methodologies have had the biggest impact on how organic compounds are made," says Eric Jacobsen, an organic chemist at Harvard University. "Cross-coupling methods are now used in all facets of organic synthesis, but nowhere more so than in the pharmaceutical industry, where they are used on a daily basis by nearly every practicing medicinal chemist."

As a result, Jacobsen and other chemists say they were not surprised by the award. "It was just a matter of time for this chemistry to be recognized," says Joseph Francisco, a chemist at Purdue University and the president of the American Chemical Society. Jacobsen says the Nobel Committee could have also chosen any of a few other cross-coupling pioneers, such as Barry Trost of Stanford University. But Nobel rules limit the committee to picking no more than three recipients. "I think they got it right," says Jeremy Berg, who heads the National Institute of General Medical Sciences in Bethesda, Maryland.

For Negishi in particular, the prize is a dream come true. After immigrating to the United States from Japan, Negishi says he had the opportunity to interact with several Nobel Laureates while studying at the University of Pennsylvania. "I began dreaming about this prize half a century ago," Negishi says. At a press conference televised in Japan, Suzuki said he hopes his work will have a similar effect on the next generation. "Japan has no natural resources. Knowledge is all we've got," Suzuki says.

–ROBERT F. SERVICE

With reporting by Dennis Normile in Tokyo.

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ScienceInsider

From the *Science* Policy Blog

A National Academies' report on how U.S. universities have **managed intellectual property** in the wake of the 1980 Bayh-Dole Act has concluded that things are pretty much hunky-dory but that schools may be trying too hard to cash in on discoveries. Universities instead should aim to disseminate technology for the public good, which may mean passing up a more lucrative licensing deal. http://bit.ly/bayh-dole-update

The U.S. Food and Drug Administration is pressing for a $25 million funding boost for research that can help it **evaluate new treatments** better and faster. Commissioner Margaret Hamburg says such "regulatory science" would allow the agency to help turn the nation's sizable investment in basic biomedical research "into vital products for those who need them." http://bit.ly/fda-research

Israel's minister of education, Gideon Sa'ar, has **fired his chief scientist** for comments that questioned the tenets of evolution and global warming. Gavriel Avital's trial appointment last December had been controversial from the start. http://bit.ly/sacked-adviser

The National Ignition Facility, the highest energy laser in the world, has fired its first shot in what officials at Lawrence Livermore National Laboratory hope will be a successful **campaign to achieve ignition**—a self-sustaining fusion burn that produces more energy than was pumped in to make it happen. http://bit.ly/first-blast

The National Institutes of Health has launched a $60 million program that will allow a few talented **young scientists to become independent investigators** shortly after earning their Ph.D.—provided they can get jobs with institutions willing to nominate them for the award. http://bit.ly/early-independence

The European Union has unveiled a new plan to foster innovation. Officials hope its emphasis on making it easier for companies to actually **use the fruits of science** will bridge a valley of death that slows commercialization. http://bit.ly/innovation-union

For more science policy news, visit **http://news.sciencemag.org/scienceinsider**.

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