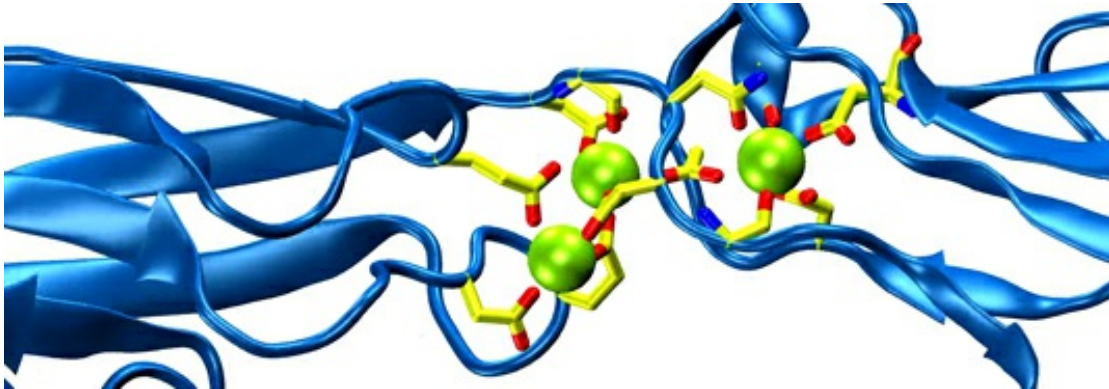


Texas Advanced Computing Center - Sound Science



A team led by Rachele Gaudet and David P. Corey used X-ray crystallography to determine the molecular structure of cadherin-23's tip, with and without a mutation causing deafness.

Sound Science

Simulations by Harvard researchers on *Ranger* show how subtle mutations cause deafness

The ear is a mighty and mysterious instrument. Tiny machinery in the cochlea transforms sound waves into electrical signals — a process called sound transduction — which the brain recognizes as our name, or a ringing telephone. Because of the mechano-sensitive actions of minute hair cells in the ear, we can hear and react to stimuli in our environment in a fraction of a second, responding to a friend, or grabbing the phone.

Scientists have had a broad understanding of sound transduction since the 1980s. However, the story of sound perception at the molecular level is just now being written. Scientists at Harvard Medical School recently resolved the first x-ray crystallographic structure of one of the main proteins active in the hearing process: cadherin-23. Cadherin pulls open the hair cell receptors to create a channel in the receptor membrane for ions to pass through. The voltage difference created by this ion transfer is what the brain understands as sound.

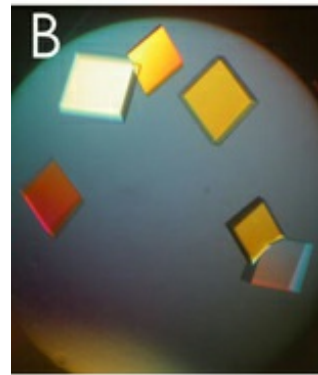
"The Corey lab focuses on how sound becomes an electrical signal," said Marcos Sotomayor, a research fellow at David Corey's laboratory in the Neurobiology Department at the Harvard Medical School. "We're trying to identify the 3D structure of the proteins involved in the transduction of sound."

Cadherin-23 is also one of the proteins that malfunctions in individuals with hereditary deafness. Scientists believe one in 1,000 individuals in the U.S. are affected by this kind of disease, and 7.5 percent of hereditary deafness cases are caused by mutations in cadherin-23.

The Harvard research team, including Sotomayor and Wilhelm Weihofen, and led by Rachele Gaudet and David P. Corey, used the *Rangers* supercomputer at the Texas Advanced Computing Center (TACC) to simulate the 3D structure of cadherin-23 obtained from x-ray data. Then, they set the protein in motion, simulating the behavior of each atom as it reacted to forces that mimicked the effect of sound waves.

"In order to understand how the protein responds to forces, we put it in the computer and stretched the protein just as would happen in the inner-ear," he said.

Cadherins involved in sound transduction. (A) Scanning electron micrograph of a hair bundle (bullfrog sacculus, D. P. Corey). (B) Crystals of cadherin-23, a protein essential for hair-cell transduction. (C) Structural model of cadherin-23 obtained through X-ray crystallography.



The team performed hundreds of simulations on *Ranger*, and learned a number of important things about cadherin-23 that challenged their initial hypothesis about the protein.

"It was assumed that these proteins would be stretchy, like a soft spring," Sotomayor explained. "Actually, they are more like a stiff wire."

The simulations also showed that some deafness-related mutations to the protein do not alter the fold and strength of cadherin-23 directly. Rather, they change the way the protein binds calcium, which ends up weakening its structure.

"While doing measurements of calcium affinity, we realized that this deafness mutation was modifying how the protein binds calcium," Sotomayor said. "The simulations showed that without calcium, the protein is weak."

According to University of Maryland biology professor and mechanoreceptor expert, Sergei Sukharev, the simulations gave rise to the "far-fetched" prediction that mutations can affect the cadherin's strength not only by changing flexibility of the linker region, but also by changing calcium affinity.

"When the need arose, the team did not stop short and performed bench experiments which confirmed this computational prediction," Sukharev said.

The change in calcium affinity makes a big difference for the mutant cadherin-23 proteins, which snap under mechanical stress, causing hearing loss. The group's findings were published in the April 2010 edition of the

Marcos Sotomayor, a research fellow at David Corey's laboratory in the Neurobiology Department at the Harvard Medical School.



"A very natural combination of crystallography with advanced computer simulations has made this study feasible and highly conclusive," said Sukharev.

"Using the supercomputer, we were able to see where the calcium is bound, how it's bound to the protein, and how it modulates the elasticity of the protein," said Sotomayor. "That's something that cannot be done with any other technique."

The simulations were the first of this important protein, which was only recently identified as part of the sound transduction apparatus, in part because hair cells from the cochlea are fragile, scarce, and notoriously difficult to work with. It wasn't until 2008 that Sotomayor and colleagues first imaged the protein using x-ray crystallography, a method of determining the position of individual atoms within biomolecules.

The team then used the NAMD (NAnoscale Molecular Dynamics) and VMD (Visual Molecular Dynamics) software packages to simulate and analyze the 3D structure of cadherin-23 in systems encompassing up to 355,000 atoms. The project used the computing and storage systems at the [National Center for Supercomputing Applications](#) (NCSA), as well as those at TACC, to complete the work. Both TACC and NCSA are part of the [TeraGrid](#), a nationwide network of academic HPC centers, sponsored by the NSF Office of Cyberinfrastructure, that provide scientists and researchers access to large-scale computing, networking, data-analysis and visualization resources and expertise.

Despite the difficulty of getting the initial data, the protein turned out to be a particularly good candidate for molecular dynamics simulations. Sotomayor's virtual experiments increased the length of the cadherin simulations to 100 nanoseconds, whereas sound transduction in the ear occurs in a few microseconds.

However, most biological processes take many milliseconds, if not seconds, so proteins involved in hearing, with their fast mechano-sensitive actions, make good candidates for analysis.

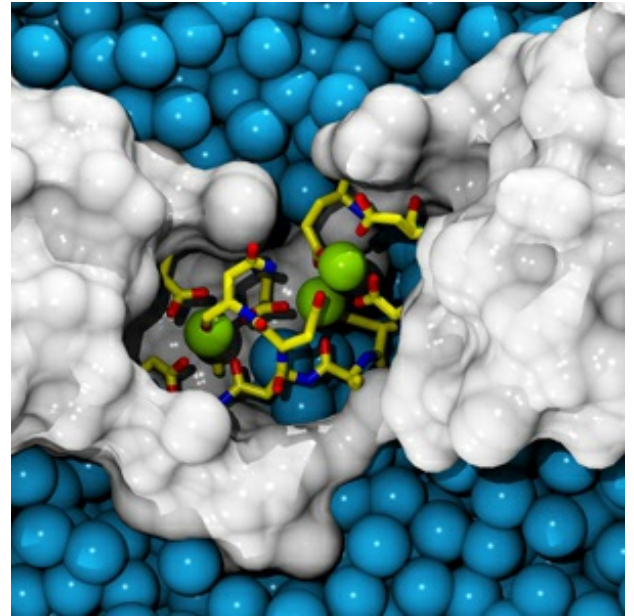
"The simulations are almost in the physiological range of time scales, and they're closer than any other simulation done before for this kind of systems," he said.

The results of the computational experiments will be validated through laboratory experiments, and hopefully the knowledge gleaned from the simulations will eventually help doctors test for, and treat, some types of deafness.

"It shows how part of sound transduction happens at the molecular level, and that's a first," said Sotomayor.

"Eventually, I think it will inform therapy, but it will probably take 10 or 20 years to do so."

Typical setup for a molecular dynamics simulation showing protein (white and colored sticks), water molecules (blue), and ions (green). [Made with VMD.]



The Future of Molecular Dynamics Simulations

With new peta- and exa-scale systems anticipated to come online in the next few years, molecular dynamics (MD) simulations are anticipating a dramatic boost.

According to Sotomayor, this explosion in computing power will have two seemingly contradictory effects on the field.

First, more computing power will allow researchers to improve the accuracy of the force fields used to model atomic interactions.

"We don't understand the effects of polarizability quite well, which is an important property of atoms neglected in most simulations," Sotomayor said. He believes the next generation of force fields will have more detailed (and more computationally expensive) descriptions of how the atoms interact with each other. This will be possible because of the upcoming increase in supercomputing power.

If the first approach makes simulations more accurate, the second approach, called coarse-grained simulation, sacrifices molecular accuracy, but reaches more realistic timescales and system sizes.

"We want to simulate larger systems for longer timescales, and we can do it by simplifying the description of the

simulated biomolecular systems and using the next generation of supercomputers," he said.

Sotomayor believes that researchers will actually apply both methods simultaneously to get the maximum insights.

"You will see simulations that mix both the atomistic description of a protein or biomolecule with a less accurate description of whatever is not directly relevant for the biological process under study," said Sotomayor.

This mixed representation will simplify parts of the description of a biomolecular system but still reserve the atomistic description for the interesting parts, greatly increasing the insights available to scientists and efficiently harvesting the computing power of machines like TACC's *Ranger*.

June 9, 2010

The Texas Advanced Computing Center (TACC) at The University of Texas at Austin is one of the leading centers of computational excellence in the United States. The center's mission is to enable discoveries that advance science and society through the application of advanced computing technologies. To fulfill this mission, TACC identifies, evaluates, deploys, and supports powerful computing, visualization, and storage systems and software. TACC's staff experts help researchers and educators use these technologies effectively, and conduct research and development to make these technologies more powerful, more reliable, and easier to use. TACC staff also help encourage, educate, and train the next generation of researchers, empowering them to make discoveries that change the world.