# TeraGrid resources help Harvard team gain insights into deafness

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*Adapted from a Harvard Medical School article*

Proteins are the machinery behind cellular processes in living organisms, and much has been learned about how they function in the perception of some external stimuli from their three-dimensional structures. However, little is known about the protein molecules involved in touch and auditory function. Now, a team from Harvard University has resolved the atomic-level structure of a protein essential for sound perception. The structure was then simulated using TeraGrid supercomputers to determine how it functions in hearing and deafness. The research was published in the April 15 issue of *Neuron*.

Sound becomes an electrical signal in hair cells of the inner ear. These cells are sensitive mechanoreceptors that are moved by sound, stretching fine filaments called "tip links" to pull open ion channels and generate electrical signals that are sent to the brain. The tip link is made of two non-classical cadherin molecules, cadherin-23 and protocadherin-15, which are defective in some forms of hereditary deafness.

A team led by Rachelle 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. Yet, static images of the protein provided little information about its function in hearing mechanics, so the team decided to test cadherin-23's elasticity using molecular dynamics simulations on TeraGrid systems at NCSA and the Texas Advanced Computing Center (TACC).

The protein structures were modeled in water boxes to mimic their biological environment; the simulation systems encompassed up to 355,000 atoms. Using the NAMD software developed by the Theoretical and Computational Biophysics Group at the University of Illinois at Urbana-Champaign, the team performed hundreds of molecular dynamics simulations using the Ranger system at TACC and the Abe cluster at NCSA. The powerful machines and large number of processors available allowed them to test the elasticity of cadherin-23's tip in multiple near-physiological conditions. Analysis of more than 5 terabytes of data generated by the simulations revealed an essential role for calcium ions in the mechanics of cadherin-23.

The protein was found to be stiff in the presence of calcium, but weak when calcium was not bound to it. A deafness-causing mutation was found to alter calcium binding to the cadherin-23 protein, thus reducing its mechanical strength and possibly making tip links prone to rupture, thereby impairing sound perception. The simulations performed at TeraGrid facilities allowed the team to get insights about the role of calcium ions and cadherin-23 mechanics in hearing and deafness that cannot be obtained with any other technique, and provided predictions that can be experimentally tested.

"The outstanding resources and support provided by the TeraGrid were essential to our work," says Marcos Sotomayor, a member of the research team at Harvard Medical School. "We were particularly happy with Ranger and Abe, as we were able to use NAMD on both machines extensively and smoothly. We also benefited from NCSA's Unitree storage system, which was essential for us as we were able to recover all our data when one of our local disks failed."

**Team members**
David P. Corey
Rachelle Gaudet
Marcos Sotomayor
Wilhelm A. Weihofen