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For Determining Protein Structures, A New Method Boosts Precision and Speed in High-Dimensional NMR

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BUFFALO, N.Y. -- A University at Buffalo chemist has developed a new, high-throughput method for obtaining nuclear magnetic resonance (NMR) data that not only has the distinction of potentially performing orders of magnitude faster than conventional methods, but does so more cheaply and with greater precision.

The new method, described in the current online issue of the Journal of the American Chemical Society, has the potential to increase greatly the use of high-throughput NMR to determine protein structures with the ultimate goal of developing new medicines and treatments.

A patent has been filed on the method and UB is exploring licensing opportunities.

"Our method allows researchers to get the information from their NMR experiments faster, while at the same time increasing accuracy," explained Thomas Szyperski, Ph.D., UB associate professor of chemistry and biochemistry and principal author.

"It's an important contribution to increasing the competitiveness of NMR relative to X-ray diffraction in structural biology," he said.

It also has the potential to allow scientists to take full advantage of the new, highest-field NMR machines and cryogenic probes, which reduce NMR measurement times by an order of magnitude (factor of 10).

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"With this new method, we've increased data collection speed by orders of magnitude," said Szyperski. "For example, for the experiment published in JACS, the gain was a factor of 250, while we increased the precision of the frequency measurements three- to four-fold.

"That's an incredible blend, which will allow us to bring the horsepower of our new 'NMR-Ferraris' equipped with cryogenic probes on the road."

Szyperski developed the method with Seho Kim, Ph.D., formerly a postdoctoral fellow in Szyperski's lab, as a member of the Northeast Structural Genomics Consortium, (NESGC) one of nine National Institutes of Health-funded efforts to capitalize on discoveries generated by the human genome project.

UB's NESGC researchers are affiliated with the Strategically Targeted Academic Research (STAR) Center in Disease Modeling and Therapy Discovery at UB, sponsored by the New York State Office of Science, Technology and Academic Research.

NMR machines use very powerful magnetic fields to determine macromolecular structures. NMR experiments provide "nuclear Overhauser enhancements," or NOE's, molecular "rulers" that allow researchers to measure distances between protons and use that information to calculate the molecular structure.

To obtain NOEs, scientists first must measure the chemical shifts, or resonance frequencies, of the atomic nuclei, which relate to the environment of each atom's nucleus. To do so, they perform several NMR spectra experiments with multiple frequency dimensions, in which resonance frequencies are measured and correlated.

According to Szyperski, when using such multidimensional NMR, the approach scientists use for determining protein structures, it is necessary to run many such experiments with higher dimensions (higher than 2D) to measure and correlate frequencies.

"Ultimately, you want a resonance assignment for each nucleus in each atom," explained Szyperski. "So for every protein, you need to have and correlate thousands of resonance frequencies.

"The drawback is that for each additional dimension you do, the data collection takes about one or two orders of magnitude longer," he said.

For example, he explained, if two-dimensional experiments take at least several minutes, then three-dimensional experiments take several hours, four-dimensional experiments take several days and five- or six-dimensional experiments would take months or years.

"The minimum measurement times explode when the dimensions are increased," said Szyperski. "That is why five- or higher-dimensional NMR experiments never have been recorded."

At the same time, he noted, the accuracy of the measurement of the resonance frequencies obtained by these long measurement times still is not very high.

Szyperski's method, called GFT NMR, for G-matrix Fourier Transform NMR, beats both drawbacks of multidimensional NMR: the long intrinsic measurement times and the low accuracy of the frequency measurements.

GFT NMR uses a G-matrix, which represents a system of linear equations, in conjunction with Fourier Transform, the mathematical operation used to process multidimensional NMR spectra.

"We record larger numbers of low-dimensional NMR spectra and using the G-matrix we can linearly combine them to retain the information of the high-dimensional experiment," said Szyperski. "This way, we can sample spectra much more rapidly and get not the resonance frequencies themselves, but multiple sums and differences of them, which gives us higher precision.

"With GFT NMR, you can record a five- or six-dimensional experiment in about an hour or even less -- all because your measurement times increase linearly, not exponentially -- with the number of dimensions you are involving," said Szyperski.

Used for proteins since the mid-1980s, NMR has been responsible for determining about 20 percent of the structures in the Protein Data Bank, the international repository of solved protein structures, whereas the other technique, X-ray diffraction, in use since 1962 for proteins, has determined 80 percent.

"In terms of maturity, you could say we're about 22 years behind X-ray diffraction when it comes to solving protein structures," Szyperski admitted.

However, he added, the combination of much more powerful 900 megahertz magnets now coming online, such as the new one at the New York Structural Biology Center, to which UB researchers will have access, and new techniques, such as his, is ushering in a new era for NMR determination of proteins.

"Our approach will allow scientists to take full advantage of the highest-field NMR machines, without having to sample many high-dimensional spectra," said Szyperski.

New cryogenic probes, such as the one that UB will be receiving in the spring, supported by both the NIH grant to the NESGC and UB funds, will provide additional speed for NMR experiments.

In collaboration with Gaetano T. Montelione, Ph.D., of Rutgers University, and principal investigator on the NESGC, Szyperski is planning to develop a software package that will expedite the calculations required when using GFT NMR experiments to produce protein structures.