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## NMR - it's a gift

A faster and more accurate approach to NMR will allow drug discovery teams to investigate protein targets with much higher throughput than previously possible thanks to US researchers.

[Thomas Szyperski](#) of the State University of New York at Buffalo says his new NMR technique is potentially orders of magnitude faster than conventional methods but is nevertheless more precise than other methods. The technique can exploit the very highest field NMR machines and the new cryogenic probes to greatly reduce measurement times. "With this new method, we've increased data collection speed by orders of magnitude," explains 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."

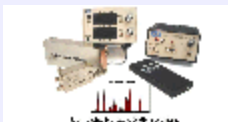


Szyperski's group is a member of the [Northeast Structural Genomics Consortium](#) (NESGC), one of nine National Institutes of Health-funded efforts to capitalize on discoveries generated by the Human Genome Project. They focused on finding a way to relax the usual constraints that arise because of the underlying principles of Fourier transform NMR - namely the excessive or even prohibitively long measurement times needed to sample indirect dimensions and the low precision of chemical shifts that can be attained from indirect dimension data because of low digital resolution. They have now turned in imprecise art that can take months, even

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years, into a precise, mathematical process that runs in a few hours or less.

Nuclear Overhauser enhancements, NOEs, are essential in probing protein structure with NMR, they essentially act as distance markers allowing researchers to measure the separations of protons and so extrapolate to a molecular structure. However, NOE measurements require the recording of several NMR spectra with multiple frequency dimensions. According to Szyperski, when using such multidimensional NMR 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," explains Szyperski. "So for every protein, you need to have and correlate thousands of resonance frequencies."

Of course, each additional dimension increases the time taken to collect the data by one or two orders of magnitude. A conventional two-dimensional experiment, for instance, takes several minutes to run. A three-dimensional experiment several hours, while a four-dimensional experiment will run over several days and even then not produce accurate results. Jump up to five- or six-dimensional experiments and obtain the necessary data to calculate the NOEs could take months or years and accuracy would be lost. Moreover, five- or higher-dimensional NMR experiments have never been recorded.

The blight of NMR spectra is a low signal-to-noise ratio. In order to achieve reliable data interpretation these must be kept as high as possible. At the same time, digital resolution has to be high to allow chemical shifts and other data to be extracted with precision. Increasing the number of dimensions does not resolve peak overlap but does eliminate ambiguities when combining several multidimensional NMR spectra are combined for resonance assignment as it raises the number of correlations obtained in a single data set. The key to reducing overall times for recording these multidimensional spectra is to aim for an adequate but not unnecessarily high S:N ratio.

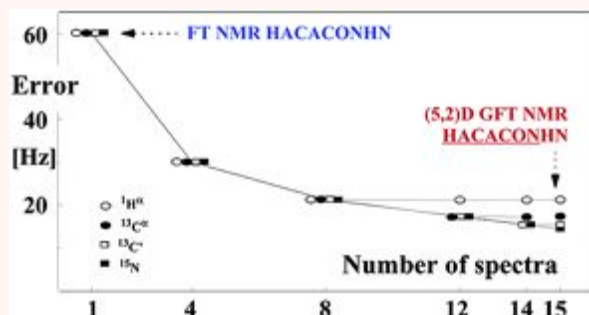
Szyperski's method - GFT NMR, for G-matrix Fourier Transform NMR - addresses both problems. A G-matrix represents a set of linear equations to combine a large number of recorded spectra. A Fourier Transform then processes the multidimensional NMR spectra to provide the desired data. "We record larger 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," says 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.



Szyperski and his team performing GFT NMR

"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. A software package to speed up the GFT calculations is being developed in collaboration with [Gaetano Montelione](#), Rutgers University, and PI of the NESG consortium.



Monte Carlo simulations performed to assess the increased precision of chemical shift measurements.

To date, NMR has revealed the structures of some 20% of the structures in the international Protein Data Bank, which Szyperski estimates puts it about 22 years behind X-ray diffraction. But, the likes of 900 MHz NMR machines that are now being put into labs could help it catch up. "It's an important contribution to increasing the competitiveness of NMR relative to X-ray diffraction (XRD) in structural biology," says Szyperski. One area that NMR will always beat XRD is, of course, in studying dynamic phenomena such as the slow folding of biological macromolecules. Where XRD takes detailed snapshots of crystalline proteins, GFT NMR will

allow researchers to watch them changing like a movie.

"Currently, only my group has implemented and is using the GFT NMR technique for assigning protein chemical shifts," Szyperski told *Spectral Lines*, but he adds, "we are currently extending the repertoire of GFT NMR experiments, it might have application in polymer science, in particular for systems with a great deal of chemical shift degeneracy."

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