Biomolecular NMR 2014

- Biomolecular NMR - short history ~ 1985 first protein structure
- Compared to X-ray ~ 1953 first protein structure
- Today ~ 11 % of structures in the PDB (10,287) come via NMR – higher for nucleic acids
- Unique structural applications – weak associations, partially structured, membrane associations, in-cell observation
- Diverse applications: drug screening, metabolic monitoring, in vivo imaging
- NMR is still an evolving science

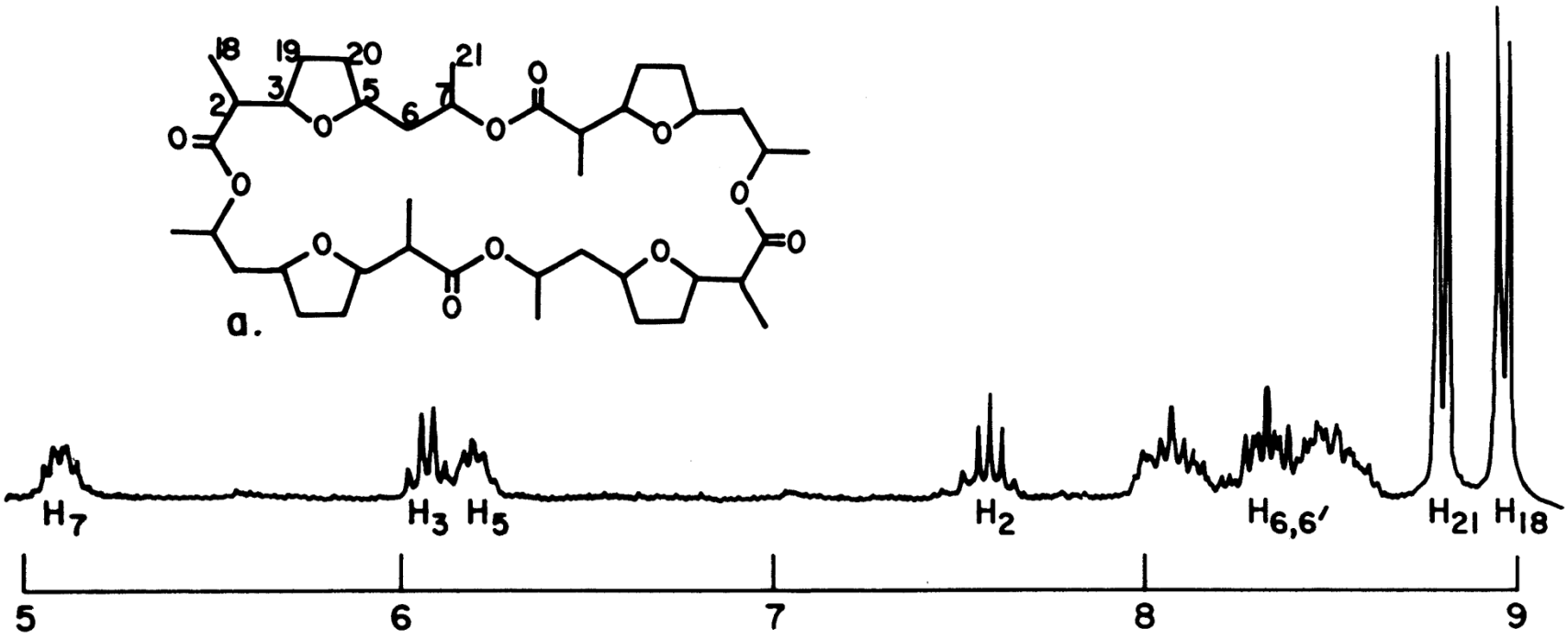
NMR Recognition

- 1944 – Isidor Isaac Rabi - Nobel Prize in Physics
  - -"for his resonance method for recording the magnetic properties of atomic nuclei"
- 1952 – Felix Bloch and Edward Mills Purcell – Nobel Prize in Physics
  - -"for their development of new methods for nuclear magnetic precision measurements and discoveries in connection therewith"
- 1991 – Richard Ernst – Nobel Prize in Chemistry
  - -"for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy"
- 2002 – Kurt Wuthrich – Nobel Prize in Chemistry
  - -"for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution"
- 2003 – Paul Lauterbur and Sir Peter Mansfield – Nobel Prize in Physiology and Medicine
  - -"for their discoveries concerning magnetic resonance imaging"

Varian HR 220

~1965
Superconducting
Magnets Boosted
Field Strength
Required a Lot of
Care And
Feeding

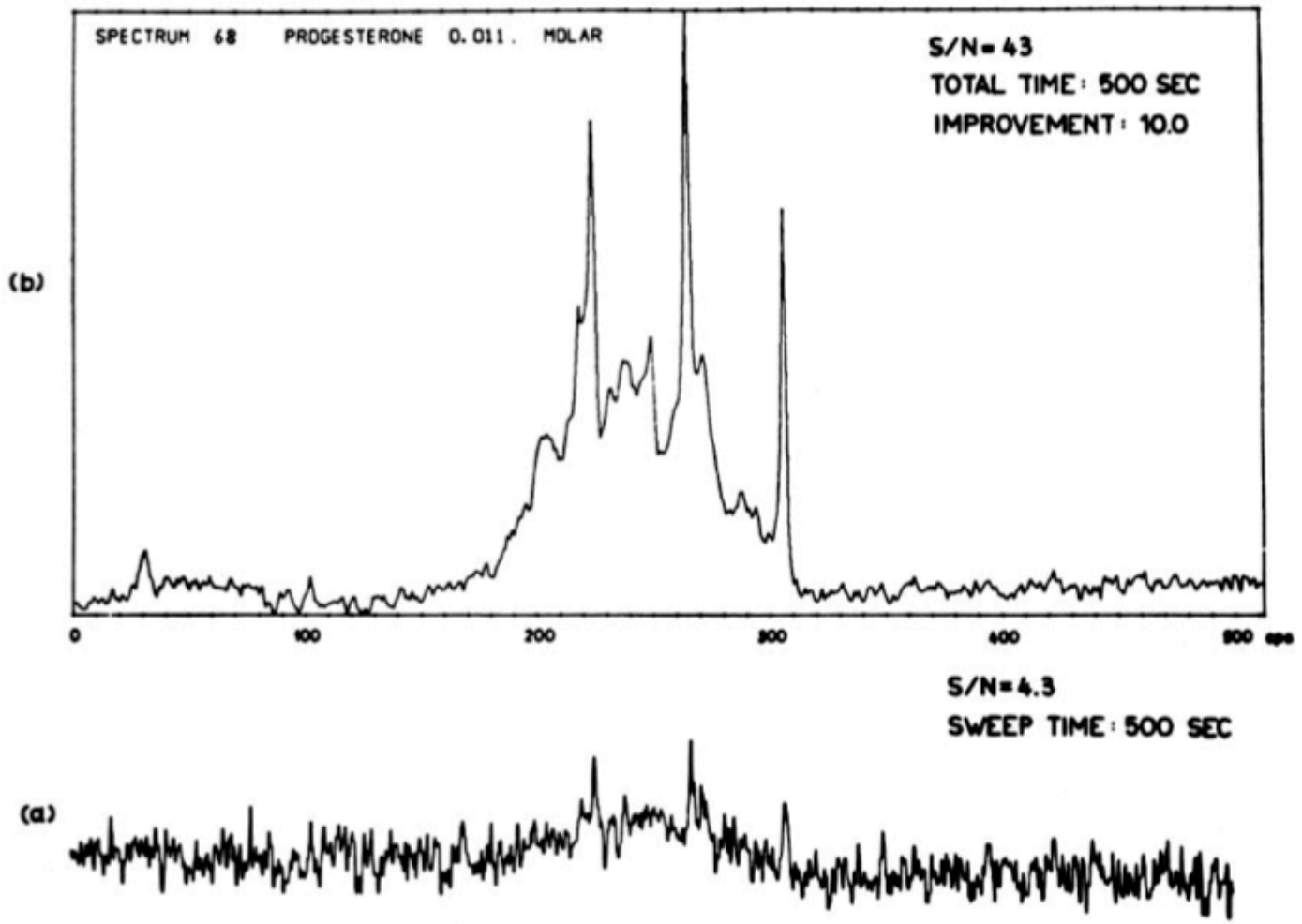
High Field (220 MHz), but Still 1D CW NMR



~1970 Richard Ernst Introduced Multidimensional Pulse FT Methods

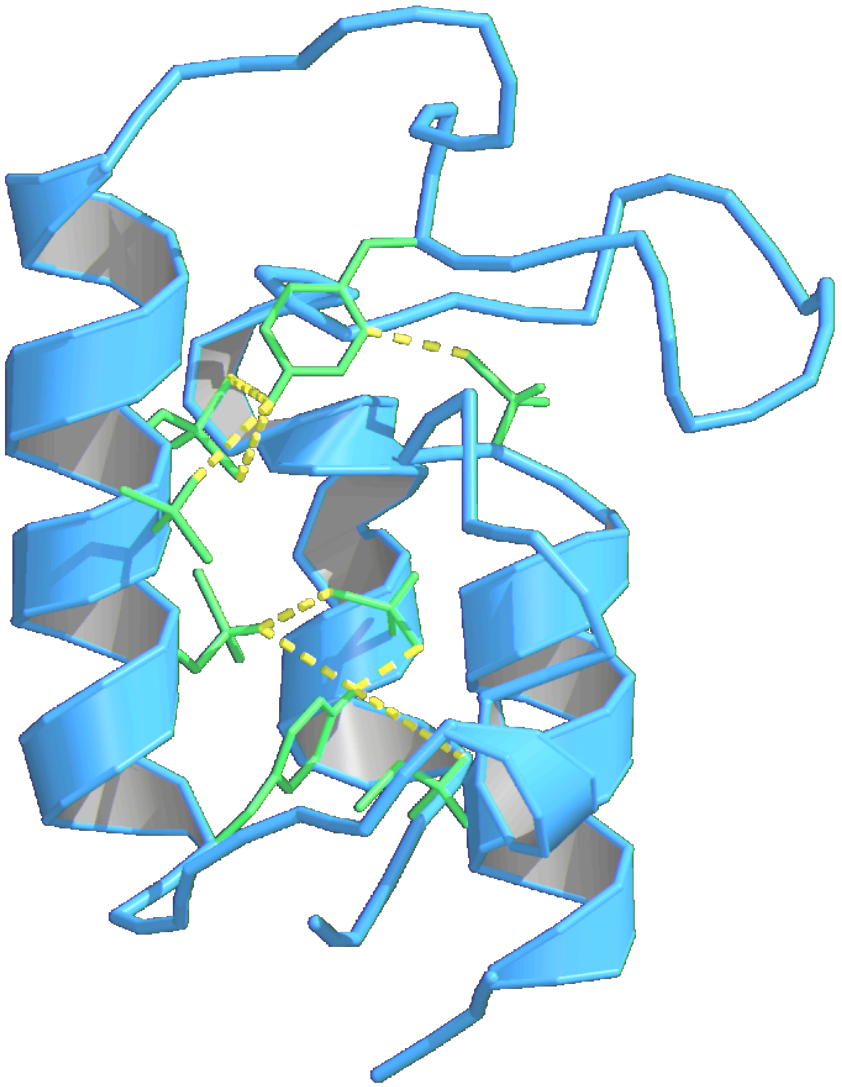
PULSED FOURIER TRANSFORM NMR

Richard Ernst & Wes Anderson, Rev. Sci. Instr. 37, 93 (1966)

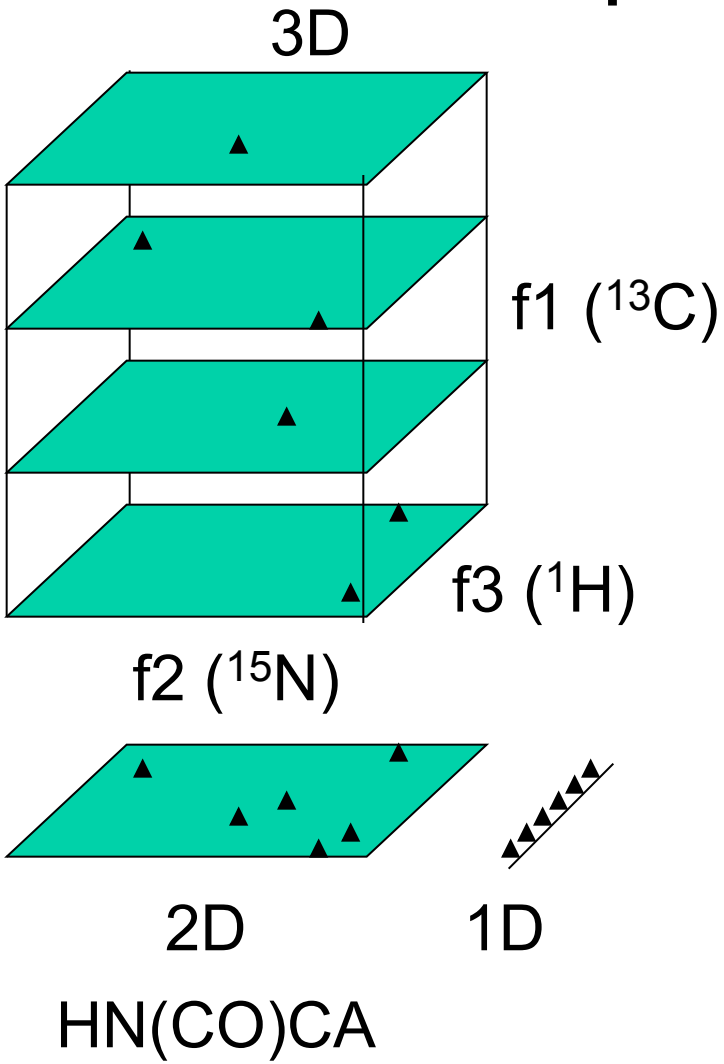


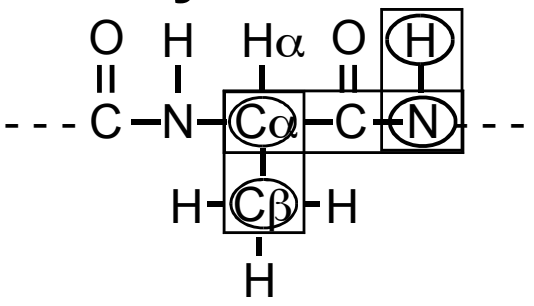
Fourier transform (top) and conventional spectra of 0.011 M progesterone showing sensitivity enhancement by a factor ten

~1982 Kurt Wüthrich: 2D ^{1}H-^{1}H NMR: ~10 kDa Protein
assign resonances, collect NOE's, calculate structure

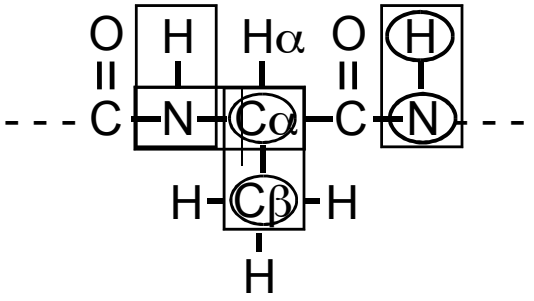


Extension to 3D: Through-bond Correlations in Peptides
Isotope Labeling is Key





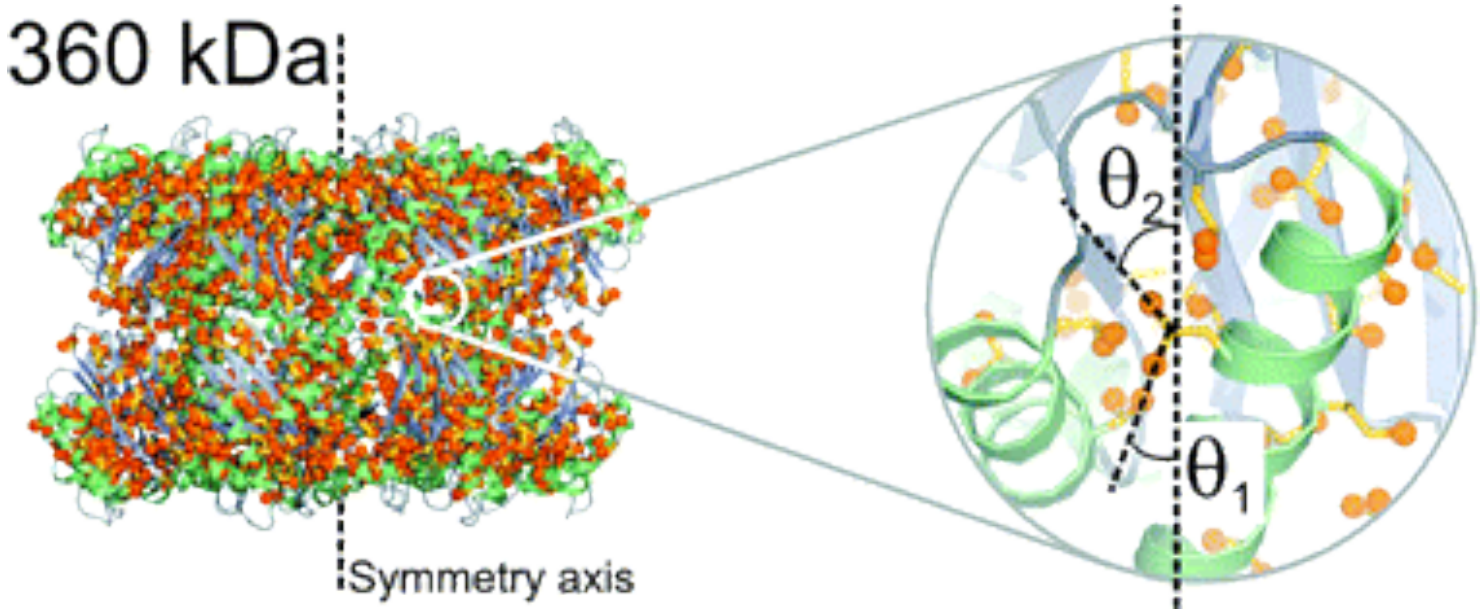
(HB)CBCA(CO)NH



HNCACB

Ikura, M.; Kay, L. E.; Bax, A., (1990) *Biochemistry* 29:4659-4667

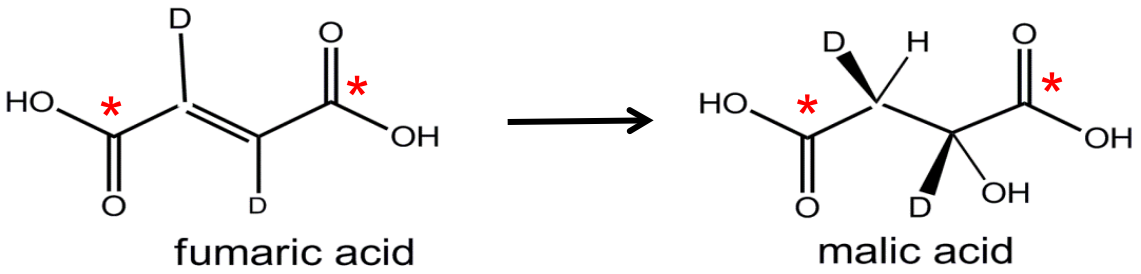
Today Very Large Systems Can Be Studied: Proteasome subunit – active site dynamics



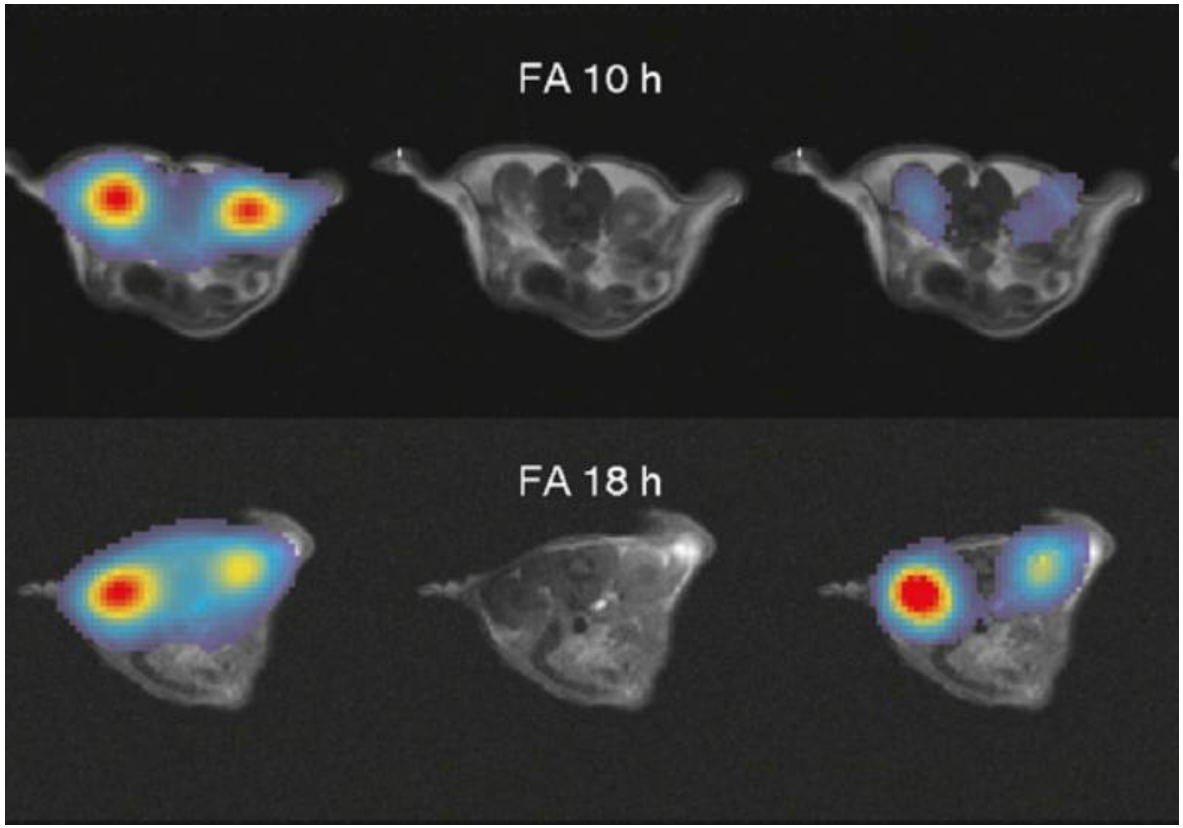
Sprangers, R and Kay, LE, 2007. Probing supramolecular structure from measurement of methyl H-1-C-13 residual dipolar couplings. *Journal of the American Chemical Society* **129:** 12668-+.

Ruschak AM and Kay LE, 2010, Methyl groups as probes of supra-molecular structure, dynamics and function, J Biomol NMR **46:**75-87

NMR Spectroscopy + MRI Monitors Metabolism *in vivo*



fumaric acid malic acid



Example: Fumaric acid to malic acid conversion indicates onset of acute tubular necrosis of the mouse kidney. Images are 10 and 18 hrs after folic acid induced nephropathy. Left and right images based on signals of carboxyl resonances of fumaric and malic acid respectively.

Kevin M. Brindle, et al. PNAS, 109, 1374-1379, 2012

NMR is widely applicable to structure and function of biomolecules

- Montelione, G. T. & Szyperski, T. (2010). Advances in protein NMR provided by the NIGMS Protein Structure Initiative: Impact on drug discovery. *Current Opinion in Drug Discovery & Development* **13**, 335-349.
- Tzeng, S. R. & Kalodimos, C. G. (2011). Protein dynamics and allostery: an NMR view. *Current Opinion in Structural Biology* **21**, 62-67.
- Felli, I. C. & Pierattelli, R. (2012). Recent progress in NMR spectroscopy: Toward the study of intrinsically disordered proteins of increasing size and complexity. Iubmb Life 64, 473-481.
- Hurd, R. E., Yen, Y. F., Chen, A. & Ardenkjaer-Larsen, J. H. (2012). Hyperpolarized 13C metabolic imaging using dissolution dynamic nuclear polarization. Journal of Magnetic Resonance Imaging 36, 1314-1328.
- Robinette, S. L., Bruschweiler, R., Schroeder, F. C. & Edison, A. S. (2012). NMR in Metabolomics and Natural Products Research: Two Sides of the Same Coin. Accounts of Chemical Research 45, 288-297.
- Gopinath, T., Mote, K. R. & Veglia, G. (2013). Sensitivity and resolution enhancement of oriented solid-state NMR: Application to membrane proteins. Progress in Nuclear Magnetic Resonance Spectroscopy 75, 50-68.
- Goldbourt, A. (2013). Biomolecular magic-angle spinning solid-state NMR: recent methods and applications. Current Opinion in Biotechnology 24, 705-715.
- Manley, G. & Loria, J. P. (2012). NMR insights into protein allostery. Archives of Biochemistry and Biophysics 519, 223-231.
- Qureshi, T. & Goto, N. K. (2012). Contemporary Methods in Structure Determination of Membrane Proteins by Solution NMR. In Nmr of Proteins and Small Biomolecules (Zhu, G., ed.), Vol. 326, pp. 123-185.
- Bardaro, M. F. & Varani, G. (2012). Examining the relationship between RNA function and motion using nuclear magnetic resonance. Wiley Interdisciplinary Reviews-Rna 3, 122-132.