Journal of Magnetic Resonance 241 (2014) 1–2

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Foreward

A special "JMR Perspectives" issue: *Foresights in biomolecular solution-state NMR spectroscopy – from spin gymnastics to structure and dynamics*

In the past several decades, the landscape of biomolecular NMR spectroscopy has been completely transformed. Solution NMR in particular, has developed from a qualitative method used to characterize small organic molecules and peptides, to a sophisticated quantitative technique that can be effectively applied to a broad spectrum of critically important biological problems. The net result is that detailed structural and motional information – with site-specific resolution – can now be obtained using NMR that beautifully complement results from other structural biology tools. As so often has happened throughout the history of NMR, these science-driven achievements are deeply rooted in new developments that, at a methodological level, continue at an unabated pace. The *Journal of Magnetic Resonance* has played throughout the decades a prominent role in encouraging synergy between physical insights and biophysical applications. In this special issue of the Journal we celebrate this tradition, by presenting a series of perspective articles on the current state of the art in biomolecular solution NMR spectroscopy written by leaders in the field.

With the development of heteronuclear bioNMR 30 years ago, it became clear that a key element in its progress would be labeling. Here molecular biology and synthesis of important precursors are critical. In the present issue *Prestegard* and coworkers present a discussion on the use of sparse labeling methods involving single or a small subset of amino acids, that becomes a particularly important option when protein expression must be achieved using non-bacterial hosts. *Kainosho* and colleagues provide a powerful example of the use of synthetic strategies for the production of suitably labeled amino acids, that are then used to study hydrogen exchange of HO-, HS- and H_2N-moieties attached to buried residues in proteins using lineshape analysis of peaks in ^{13}C spectra.

NMR has always been limited by the need for improved sensitivity. This can be achieved through the use of new experimental approaches that include the ever-popular TROSY-based schemes, but also by the development of new methods that decrease the tumbling times of solutes by immersing them into the aqueous interior of reverse micelles that are dissolved in low viscous fluids. *Wand* and coworkers review the current advances in this area. Sensitivity increases can also be obtained using a variety of methods including DNP, photo-CIDNP, parahydrogen-induced polarization and optical pumping that are finding important uses in biological studies. *Cavagnero* and colleagues provide an up-to-date review of these areas. Hand-in-hand with the need for more signal-to-noise is also the importance of increasing resolution. *Bax* and coworkers provide a simple approach for achieving this goal whereby band selective homonuclear (^1H) decoupling is applied during ^1H acquisition in data sets, significantly improving resolution in the amide region of protein spectra. Applications to NOESY experiments and residual dipolar coupling measurements are also provided to illustrate the benefits of this method. An alternative, albeit more expensive, approach for improving resolution is to work with bigger magnets. Exploiting the inherent resolution that is afforded by these higher field spectrometers is best achieved through the use of non-uniform sampling schemes, and by suitable reconstruction methods tailored to the application in hand. *Wagner* and coworkers provide a cogent review of the approaches that are available and illustrate the benefits over standard uniform sampling and Fourier transfer methods.

NMR has long been a powerful technique for studies of molecular dynamics over a broad spectrum of time-scales and it is becoming increasingly clear that biological function is predicated on excursions between different conformations. *Palmer* provides a nice summary of the tool-box of methods that are available for studies of chemical exchange in biomolecules, including applications that stress the utility of the different experiments. The fact that biomolecules are not static has important implications for how structures are calculated and, in turn, represented. *Riek* and colleagues provide a summary of their novel approaches for generating ensembles of protein conformers that provide a more accurate representation than a single structure. A relatively new area for structural biology is "unstructural biology" that has been spearheaded by studies of intrinsically disordered proteins (IDPs). Here too, dynamics are obviously critical, and NMR is well poised to make very valuable contributions in this area. The importance of IDPs is underscored by the fact that four articles in this issue are dedicated to this topic, including contributions from the laboratories of *Sklenar*, *Konrat*, *Felli* and *Skrynnikov*. A central theme that emerges is the continued need both for novel NMR methodology that addresses the limited chemical shift resolution in spectra of IDPs and the development of computational approaches to properly take into account the averaged structural parameters that are measured on systems that are clearly dynamic ensembles of conformers.

NMR studies have traditionally focused on relatively small biomolecules and molecular complexes, although this is changing rapidly with the development of new labeling approaches, pulse sequence methodology and increased spectrometer fields. One area that has emerged is the study of membrane proteins and the importance of dynamics in regulating function in this very

http://dx.doi.org/10.1016/j.jmr.2014.01.010
1090-7807/

important class of biomolecule. *Shimada* and coworkers provide a current account of exciting developments in this area. The need for combining NMR with other structural biology tools is made very clear in the excellent review by *Carlomagno* focusing on applications to RNA-protein complexes. It remains clear that experimental restraints are limiting in NMR studies of high molecular weight complexes where the need for integration of data from a variety of different experimental sources becomes paramount. Computational approaches are therefore critically important, as discussed in the review by *Van Ingen* and *Bonvin*.

We would like to use this opportunity to thank all our contributors for their timely and comprehensive views on a variety of important areas in biomolecular NMR spectroscopy. We would also like to appreciatively dedicate this compilation to our colleague Professor Christian Griesinger. We all know Christian as an outstanding scientist; in addition to his legendary figure as ''bioNMR sorcerer'', Christian has provided in the past and continues to provide many outstanding services to our community. One such example has been Christian's commitment to the Journal of Magnetic Resonance, for which he served as Associate Editor over the 1997-2013 period with the handling of over 1400 submissions! To Christian, as he steps down from this role, we extend a sincere thank you and wishes for continued productivity in science and success and happiness in all walks of life. We hope that we can count on your wisdom and sage advice for many years to come, as member of our Editorial Board. And to the rest of us NMR practitioners: we trust you will find the articles included in this Special Issue stimulating, and we look forward to your feedback and suggestions for improving the service that JMR provides to the biomolecular NMR community.

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