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Historical Perspective

Gradient enhanced spectroscopy

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ABSTRACT

This paper provides a brief overview of the personal recollections of the authors regarding their contributions to the introduction of shielded gradient technology into NMR spectroscopy during the late 1980s and early 1990s. It provides some background into early probe design and details some of the early technical progress with the use of shielded magnetic field gradients for coherence selection in high resolution NMR and describes the developments at General Electric, the National Institutes of Health, Georgetown University and Johns Hopkins University School of Medicine that ultimately led to this technology becoming commonplace in modern NMR spectroscopy. Most of this early technical work was published in the Journal of Magnetic Resonance.

Interview with the author(s).

A video interview with the author(s) associated with this Historical Perspective and the original article can be found in the online version, at doi:10.1016/j.jmr.2011.08.018.

(Peter) In 1987 I switched fields from NMR to MRI and started working for Jack Cohen at NIH, where I also met Chrit Moonen. *In vivo* MR was exciting because it opened up a new world of tools and applications. Coming from high resolution NMR, a field dominated by phase cycling, it was breathtaking to experience the power of using magnetic field gradients not only for imaging, but also for water suppression and other types of coherence selection. Even though our main focus was *in vivo* NMR, Chrit and I had not forgotten our earlier NMR training; therefore, we set out on some side activities to use gradient technology for high-resolution solution state applications. At a General Electric (GE) training course in 1988, we met Ralph Hurd, another convert from high-resolution NMR who had started to use gradients for multiple-quantum experiments, using the acronym of gradient-enhanced (GE) NMR.

(Ralph) Although we had not yet referred to the method as such, Dominique Freeman and I had been using *gradient-enhanced* double quantum COSY to edit for lactate, *in vivo,* on a preclinical 2T MR scanner in the late 1980s [1]. The opportunity to extend this technology back to high-resolution NMR came with the introduction of an *in vivo* option for the vertical WB 400 system, which included shielded gradients. Although the initial RF probes designed to fit in these gradient sets were primitive from high-resolution NMR standards (no lock, no heater, no spinner and more appropriate for mice than macromolecules – see Fig. 1), we were able to obtain high-resolution gradient-enhanced DQ-COSY and TOCSY results which I submitted as a communication to JMR in late 1989 [2].

(Peter) In 1990, we separately submitted abstracts to the Experimental NMR Conference (ENC) demonstrating the application of field gradients for the study of macromolecules [3,4]. Although the use of field gradients for coherence selection had been suggested earlier [5,6], the development of shielded gradients for MRI [7] had now allowed its first practical applications. Chrit and I followed up with papers in JMR using diffusion [8], and gradient coherence selection [9] for water suppression.

(Ralph) In 1990, following the success Peter and I had at the ENC as the "gradient twins", I teamed up with Boban John, Dan Plant, Paul Calderon and others at GE to extend gradient-enhanced technology to proton-detected heteronuclear, 3D and phase sensitive applications, as well as work on the design of *real* high-resolution gradient probes. This work progressed nicely over the next 2 years as we explored new applications and improved gradient technology for high-resolution NMR spectrometers [10–18]. We were very fortunate to be able to document our advances throughout that period of time in the Journal of Magnetic Resonance.

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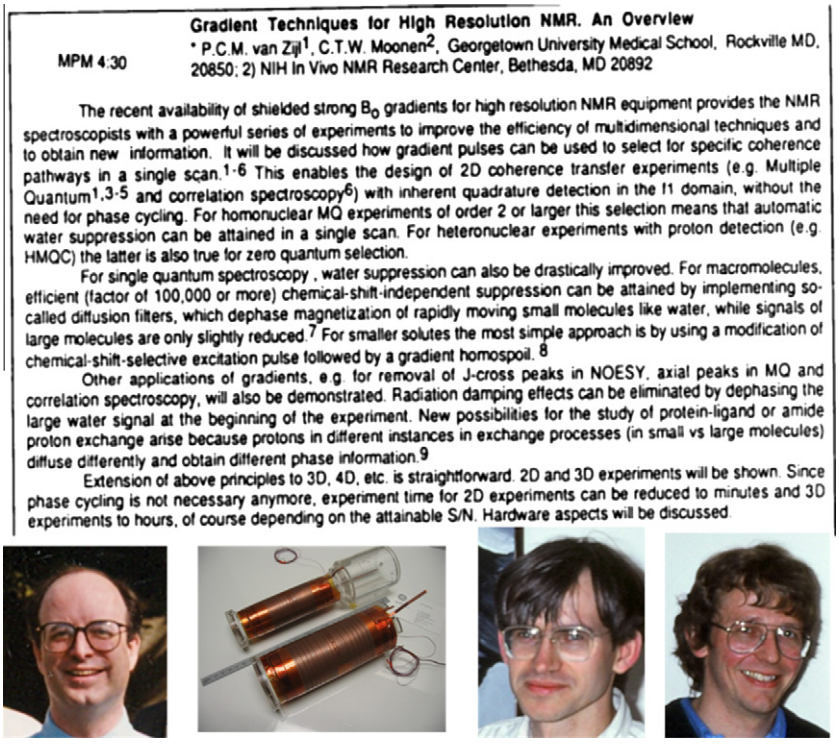

Gradient Techniques for High Resolution NMR. An Overview

MPM 4:30

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The recent availability of shielded strong B_0 gradients for high resolution NMR equipment provides the NMR spectroscopists with a powerful series of experiments to improve the efficiency of multidimensional techniques and to obtain new information. It will be discussed how gradient pulses can be used to select for specific coherence pathways in a single scan.[1-6] This enables the design of 2D coherence transfer experiments (e.g. Multiple Quantum[1,3-5] and correlation spectroscopy[6]) with inherent quadrature detection in the f1 domain, without the need for phase cycling. For homonuclear MQ experiments of order 2 or larger this selection means that automatic water suppression can be attained in a single scan. For heteronuclear experiments with proton detection (e.g. HMQC) the latter is also true for zero quantum selection.

For single quantum spectroscopy , water suppression can also be drastically improved. For macromolecules, efficient (factor of 100,000 or more) chemical-shift-independent suppression can be attained by implementing so-called diffusion filters, which dephase magnetization of rapidly moving small molecules like water, while signals of large molecules are only slightly reduced.[7] For smaller solutes the most simple approach is by using a modification of chemical-shift-selective excitation pulse followed by a gradient homospoil.[8]

Other applications of gradients, e.g. for removal of J-cross peaks in NOESY, axial peaks in MQ and correlation spectroscopy, will also be demonstrated. Radiation damping effects can be eliminated by dephasing the large water signal at the beginning of the experiment. New possibilities for the study of protein-ligand or amide proton exchange arise because protons in different instances in exchange processes (in small vs large molecules) diffuse differently and obtain different phase information.[9]

Extension of above principles to 3D, 4D, etc. is straightforward. 2D and 3D experiments will be shown. Since phase cycling is not necessary anymore, experiment time for 2D experiments can be reduced to minutes and 3D experiments to hours, of course depending on the attainable S/N. Hardware aspects will be discussed.

Fig. 1. Abstract for the first ENC gradient NMR lecture in 1991, where we listed as many applications as possible. Also shown from left to right: Ralph Hurd, the first set of actively shielded gradients for the GE vertical bore spectrometer, Chrit Moonen, and Peter van Zijl. Reproduced, with permission from "Van Zijl, Peter C.M.: My Life in NMR and MRI, An Ongoing Story of Serendipity" in Encyclopedia of Magnetic Resonance, eds-in-chief R.K. Harris and R.E. Wasylishen, John Wiley: Chichester. doi:10.1002/9780470034590.emrhp1049.

(Peter) At the end of the 1980s, GE Fremont was still making vertical-bore NMR spectrometers and Ralph had convinced the management to make some high-resolution probes with gradients. In 1990, Jack Cohen moved to Georgetown University and was kind enough to take me with him. Because we needed an NMR scanner to study perfused cancer cells [19], Jack bought a GE 400 MHz wide bore spectrometer with a gradient probe. This allowed us to develop the gradient-enhanced versions of water suppressed COSY, heteronuclear single quantum coherence (HSQC) and multiple quantum coherence (HMQC) spectroscopy and to describe the theory of gradient coherence selection [20–23]. Of course we send the technical papers to JMR, which was and remains the leading journal for technical development in NMR and where the reviewers provide the most useful comments. Chrit and I subsequently published a paper in JMR on pulsed gradients for exchange spectroscopy [24], and we wrote an early review on water suppression, in which most methods now included pulsed gradients [25]. I also became a GE consultant and in subsequent years, Ralph and I worked closely together and published several papers. In 1991, I gave an overview talk at the ENC about the potential of using gradients for high resolution NMR. Results obtained at NIH, Georgetown and GE were presented on topics ranging from homonuclear and heteronuclear coherence selection to exchange spectroscopy, diffusional water suppression, and suppression of radiation damping (Fig. 1) [26]. In the hall of the hotel in St. Louis, GE displayed a giant banner exclaiming the use of gradients for high resolution NMR and the GE booth was overrun by curious ENC attendees.

(Ralph) For the most part, the high-resolution gradient application work had always been a side project, but by the middle of 1991, this topic had taken a substantial part of my attention, and more importantly, the business had taken it seriously, extending the 3-axis shielded gradient technology to narrow bore systems. The resulting gradient probe design was a heroic effort in scale and thermal management, and won our mechanical engineer Paul Calderon a 1992 R&D Magazine Top 100 award.

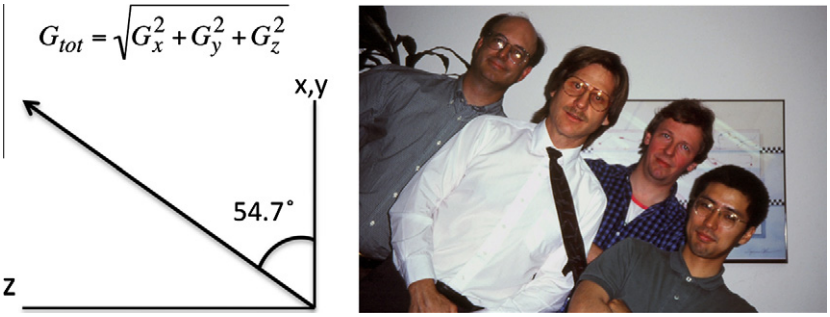

Fig. 2. To illustrate the principle of magic angle gradients, Ralph Hurd, Mark O'Neil-Johnson, Peter van Zijl and Susumu Mori pose at 54.7 degrees in 1995. Reproduced, with permission from "Van Zijl, Peter C.M.: My Life in NMR and MRI, An Ongoing Story of Serendipity" in Encyclopedia of Magnetic Resonance, eds-in-chief R.K. Harris and R.E. Wasylishen, John Wiley: Chichester. doi:10.1002/9780470034590.emrhp1049.

(Peter) The sky seemed the limit, but in 1992 our rapid progress was suddenly threatened by the decision of GE to sell its high-resolution NMR branch to Bruker. At the same time I was offered a position in the MRI Division of the Radiology Department at Johns Hopkins University and I moved to Baltimore. Two serendipitous events happened that allowed us to continue the gradient work. First, Jack Cohen decided to move on from Georgetown, leaving the GE 400 MHz scanner unused. I negotiated a good price and asked our chairman Dr. William Brody to buy it, which he did. Second, Bruker was to be conveniently located in the same building as the GE branch for *Clinical* MR spectroscopy in Fremont, where Ralph was in charge. I became a Bruker consultant for developing gradient-based pulse sequences and we continued our work, this time with Mark O'Neil Johnson, who programmed all of the gradient software on a Bruker system that was not yet configured for it. It was great fun leading to several papers in JMR, including advances on the use of magic angle gradients [27] (Fig. 2), a principle introduced theoretically by Warren et al. [28], and gradient shimming using 18 shims within a few minutes [29,30].

(Ralph) In 1992, my group was focused on developing automated *in vivo* spectroscopy for Signa™, the GE clinical MR scanner [31], and was not part of the sale to Bruker. However, with the completion of the sale, access to GE high-resolution NMR spectrometers, and internal high-resolution NMR collaborators, like Boban John, were gone. Fortunately, as Peter said, co-location of my 1.5T clinical scanner site, with the Bruker West coast facility, provided me the opportunity to continue some of the gradient-enhanced development. Again this was a sideline to my primary responsibilities at GE, and was really only possible because of the focus Peter brought as a Bruker consultant and the co-location of the GE MR Spectroscopy laboratory at the time.

(Peter) Gradually, the specialists in high-resolution NMR took over these developments and by the end of the 1990s, shielded gradients had become a staple in the hardware of high-resolution spectrometers, a grateful gift back from the *in vivo* world to basic NMR science, where the field had originated.

Note: The above dialogue contains some quotes that were reproduced with permission from "Van Zijl, Peter C.M: My Life in NMR and MRI, An Ongoing Story of Serendipity" in Encyclopedia of Magnetic Resonance, eds-in-chief R.K. Harris and R.E. Wasylishen, John Wiley: Chichester. doi:10.1002/9780470034590.emrhp1049.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jmr.2011.08.018.

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