***General MR Methods and Applications***

40 years' experience with magnetic resonance, and over 30 years of research in magnetic resonance imaging (MRI) and spectroscopy (MRS) of the human brain, heart, skeletal muscle, spine, prostate and liver. Main areas of activity over this time have been in the development of advanced MRS methods in terms of acquisition and data evaluation schemes, their applications in clinical research, but also in efforts to make these methods more robust for clinical use focusing on artifact detection, error estimation and worldwide consensus efforts, where I have been instrumental in forming the ISMRM MRS study group, writing clinical and methodological consensus papers and also spearheading a recent special issue in NMR Biomed on consensus papers covering most aspects of advanced MRS methodology.

Initial applications were for neurologic diseases and diabetes, later we also specialized in evaluating the flexibility of ectopic lipids and most recently turned to microstructure analyses with diffusion-based sequences. One focus area in the last decade has been to make use of more and more prior knowledge and in combining multiple sets of data for increased information content, accuracy, and stability of the measurements. This included the use of simultaneously acquired water signals, which is very helpful for quantitative assays but also allowed to better analyze the downfield part of the spectrum where we started work in the 90s when evaluating the phenylalanine signal that is crucial in phenylketonuria and continued with work on non-water-excitation and non-water suppression techniques finally leading to the latest publication on quantifying $NAD^+$ on clinical MR systems.

***NMR and multidimensional NMR methods in vivo:***

The first contact with magnetic resonance research was during the master thesis completing chemistry studies helping in developing ENDOR (electron-nuclear double resonance) methods in the lab of Prof Arthur Schweiger at ETH, Zurich. Subsequently, during the PhD in the lab of later Nobel-prize laureate Richard Ernst at ETH Zurich novel zero-field NMR techniques (1), a specialty of solid-state NMR, were at the focus, including multi-dimensional NMR, methods that were later transferred in the form of multidimensional MRS to in vivo examinations (2). The 2D concept was then generalized into multidimensional experiments with simultaneous evaluation in the measurement domain, rather than as dealing with multidimensional frequency spaces (3, 4).

***Early clinical MRS:***

During a post-doctoral fellowship at HMRI/Caltech, I was at the right institution with a highly experienced, motivated and expert medical doctor (Brian D Ross) when proton MRS with short

echo times became feasible in humans on clinical scanners. I helped develop these techniques, optimize their robustness, and devise proper evaluation tools for reproducible quantitative assays (5, 6). We managed to publish methodology as well as pioneering applications in multiple diseases in spite of substantial skepticism from clinical journals. Main foci were hepatic encephalopathy (5), diabetes mellitus, hypoxic injuries (7) and early brain development (8).

***Specialized methodology and applications of MRS as developed in Bern:***

In Bern, we concentrated on one hand a lot on MRS evaluations in skeletal muscle, the heart and the liver in the context of obesity and the metabolic syndrome where the base were laid for understanding muscle spectra in terms of lipid content (9) and complicating features such as residual dipolar coupling (2), susceptibility shifts (9) or effects of exercise on the spectral appearance of metabolites. Other focal points that emerged were methods for better quantitative estimations of metabolite content (4) and other metabolite properties, such as diffusion (10) or exchange phenomena. The quantitation efforts also included proper understanding (11) and management (12) of artefacts.

***Extension of MRS to the downfield part of the spectrum:***

Starting with early studies on phenylketonuria (PKU), where phenylalanine (Phe) is the major metabolite of interest with the main peak appearing in the downfield spectrum and continuing with multiple investigations on course or management of this disease (13), we specialized on the downfield metabolites in general and investigations on exchange phenomena that influence the spectral intensity of affected peaks. We developed methods that did not require water presaturation (14) or even water excitation (15) and studied the downfield spectrum with attempts to assign the spectral features at field strengths ranging from 1.5 (13) to 9.4 T (14). Recently, it was shown that the downfield resonances of $NAD^+$ can be quantified in clinical scans at 3 T (16).

References


1. Kreis R, Thomas A, Studer W, and Ernst RR. Low-frequency pulse excitation in zero-field magnetic resonance. *J Chem Phys* **89**: 6623-6635 (1988)
2. Kreis R, and Boesch, C. Spatially localized, one- and two-dimensional NMR spectroscopy and in vivo application to human muscle, *J. Magn. Reson. Series B* **113**: 103-118 (1996)
3. Kreis R, Slotboom J, Hofmann L, Boesch C. Integrated data acquisition and processing to determine metabolite contents, relaxation times, and macromolecule baseline in single examinations of individual subjects. *Magn Reson Med* **54**:761-768 (2005)
4. Rizzo R, Kreis R. Multi-echo single-shot spectroscopy combined with simultaneous 2D model fitting for fast and accurate measurement of metabolite-specific concentrations and $T_2$ relaxation times. *NMR Biomed* **e5016** (2023) (doi.org/10.1002/nbm.5016)

5. Kreis R, Farrow NA, and Ross BD. Localized $^{1}$H NMR spectroscopy in patients with chronic hepatic encephalopathy: Analysis of changes in cerebral glutamine, choline and inositols. *NMR Biomed* **4**: 109-116 (1991)
6. Kreis R, Ernst T, and Ross BD. Absolute quantitation of water and metabolites in the human brain. Part II: Metabolite concentrations. *J Magn Reson B* **102**: 9 (1993).
7. Kreis R, Arcinue E, Ernst T, Shonk TK, Flores R, and Ross BD. Hypoxic encephalopathy after near-drowning studied by quantitative $^{1}$H-magnetic resonance spectroscopy: Metabolic changes and their prognostic value. *J Clin Invest* **97**: 1142-1154 (1996)
8. Kreis R, Ernst T, and Ross BD. Development of the human brain: In vivo quantification of metabolite and water content with proton magnetic resonance spectroscopy. *Magn Reson Med* **30**: 424-437 (1993)
9. Boesch C, Slotboom J, Hoppeler H, and Kreis R. In vivo determination of intra-myocellular lipids in human muscle by means of localized $^{1}$H-MR spectroscopy. *Magn Reson Med* **37**: 484-493 (1997).
10. Döring A, Kreis R. MR spectroscopy extended by oscillating diffusion gradients as a probe for investigation of cell-specific human brain tissue microstructure. *Neuroimage* **202**: 116075 (2019)
11. Kreis R. Issues of spectral quality in clinical $^{1}$H-magnetic resonance spectroscopy and a gallery of artifacts. *NMR Biomed* **17**: 361-381 (2004).
12. Kyathanahally SP, Döring A, Kreis R. Deep learning approaches for detection and removal of ghosting artifacts in MR spectroscopy. *Magn Reson Med* **80**: 851-863 (2018).
13. Pietz J, Kreis R, Rupp A, Mayatepek E, Rating D, Boesch C and Bremer HJ, Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. *J Clin Invest* **103:** 1169-1178 (1999).
14. Fichtner ND, Giapitzakis IA, Avdievitch N, Mekle R, Zaldivar D, Henning A, Kreis R. In vivo characterization of the downfield part of 1H MR spectra of human brain at 9.4T: Magnetization exchange with water and relation to conventionally determined metabolite content. *Magn Reson Med* **79**: 2863-2873 (2018)
15. Dziadosz M, Bogner W, Kreis R. Non-water-excitation MR spectroscopy techniques to explore exchanging protons in human brain at 3 T. *Magn Reson Med* **84**: 2352–2363 (2020)
16. Dziadosz M$^{\#}$, Hoefemann M$^{\#}$, Döring A, Marjańska M, Auerbach EJ, Kreis R. Quantification of $NAD^{+}$ in human brain with $^{1}$H MR spectroscopy at 3 T. *Magn Reson Med* **88**: 1027-1038 (2022)