Foreword

Few branches of spectroscopy match the versatility, applicability and implications of Magnetic Resonance. In its molecular analysis mode, NMR, it provides structural and dynamic information in the widest range of situations: solids, organics, pharmaceuticals, proteins and nucleic acids, cells, and metabolism in living organisms. In its imaging mode, MRI, it provides one of the most widely used forms for understanding biological function and for non-invasive diagnosis of disease. A common denominator of nearly all contemporary NMR and MRI experiments relates to their need to unravel complex, overlapping information. This challenge is solved *via* one of magnetic resonance's most insightful propositions: the multidimensional NMR/MRI experiment. By spreading and correlating information onto several dimensions, multidimensional NMR/MRI stands as one of the intellectual jewels of modern spectroscopy. While originally proposed by Jeener as a tool to assign *J*-coupled peaks in a spectrum, Ernst and others rapidly realized the value of multidimensional magnetic resonance to obtain images of opaque objects, to detect invisible coherence states, to provide the resolution needed to elucidate complex chemical systems, and to determine the spatial structure of biological machines under near physiological conditions. Multidimensional approaches have since been adopted by other branches of spectroscopy—electron paramagnetic resonance, mass spectrometry, IR and visible optics—and thereby taken an additional number of unique roles in chemistry and biochemistry. But in no area of scientific research have multidimensional experiments retained such central roles as in NMR and MRI. Just to give an idea of the breadth of these applications, suffice it to mention that 2D-mediated observations of radiation-less multiple-quantum transitions is essential to understand the structure of complex materials, that 2D correlations between distant nuclei in small molecules often serve as the ‘‘eyes'' with which organic and pharmaceutical chemists identify their

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products, that correlations of low-γ evolutions with ^{1}H spin detection have been essential to endow NMR with the sensitivity needed by the structural biologist seeking to understand biochemical function *in situ*, that tens of millions of yearly 3D MRI scans are at the core of radiological exams preventing and treating the widest range of maladies, and that neither biology's nor psychology's contemporary understanding of living bodies and minds would stand where they do today without multidimensional functional MRI correlations.

Despite these invaluable and extraordinarily diverse roles of one and the same experiment, a grand challenge stands in the road of these MR implementations: the additional time that multidimensional experiments demand *vis-à-vis* their 1D counterparts. This is a demand that was ''built-in'' and accepted from the genesis of these methods onwards, but which is often onerous and far from inconsequential. Indeed, extended acquisitions have a penalty that goes far beyond the ''time is money'' concept: by increasing their duration in a manner that grows exponentially with the number of dimensions involved, high-dimensional experiments on the complex systems on which they are most essential rapidly become incompatible with their practical realization. Complex systems tend to have a dynamics of their own, and can rarely withstand extremely long examinations in their natural conditions. In few instances did this become as apparent as in the medical applications of MR, where it was clear that often infirm patients could not be subject to high-definition three- or four-dimensional acquisitions lasting for hours on end. This triggered a slow but steady departure from the discrete Fourier transform principles that dominated the *n*D MRI acquisition over its first two decades. To this end, phycisists joined efforts with computer scientists, leading eventually to the kind of sparse sampling techniques that nowadays enable the delivery of 256^3 or 512^3 3D images in a matter of minutes. These principles are finding an increased translation into NMR experiments, suffering as they do from the additional sensitivity penalties associated with lower spin concentrations and to mixing processes that, active in-between the various dimensions, tax this kind of acquisition even further. The results of these efforts within the field of NMR, particularly as they have shaped over the last decade, are summarized in the pages of this monograph. These include the use of fast-switching gradients to unravel indirect spectral dimensions, the introduction of regularization procedures in order to bypass the otherwise overtly strict sampling demands of the fast Fourier transform algorithm, the joint sampling of multiple dimensions in a ''back-projected'' fashion, and the design of metrics to assess the reliability of all these techniques. Coming to the aid of the much lower sensitivities characterizing NMR *vis-à-vis* MRI are relaxation-enhanced methods, which over recent years have become an indispensible tool in multidimensional biomolecular NMR.

While it is clear that accelerated *n*D NMR acquisitions are rapidly become a mature topic, I would like to challenge the reader by venturing to say that their final form is far from settled. Additional improvements and combinations of new spin physics and data processing will surely keep enhancing the performance of high-dimensional NMR, including perhaps spectroscopic-oriented analogues of common MRI modalities, such as multiband excitations and parallel receiving, which so far have not received all the NMR attention they might deserve. Furthermore, it is unlikely that one single approach will fit best the hundreds of multidimensional experiments normally used in solid and solution phase NMR—a diversity that in both dimensions and interactions is much higher than that occupying our MR imaging colleagues. I therefore conclude by thanking the authors and editors of this volume for offering its material as timely ''food for thought'', while encouraging all of us to read these pages with a critical, open mind. Chances are that the ultimate treatise on fast multidimensional NMR still remain to be written...

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