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Indirect detection in solid state NMR: An illustrious history and a bright future

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Many of us have a love/hate relationship with nuclear magnetic resonance (NMR). We love the information content of NMR data, which provides us with essential information about structure, dynamics, and material properties that is not available from any other measurement, and we love the fact that NMR methods can be applied to almost any problem in almost any area of science. But we hate the low sensitivity of NMR, which forces us to make big samples, spend many tedious hours or days taking data, or live with marginal signal-to-noise.

It is interesting to recognize that, at least to some extent, the high information content and the low sensitivity of NMR go hand-in-hand, with both features arising from the relative weakness of the interactions between nuclear magnetic moments and their environment. The weakness of these interactions allows us to record NMR spectra of individual isotopes within their characteristic spectral windows, leads to long relaxation times and sharp lines, allows us to manipulate spin couplings with an endless variety of pulse sequences, and leads to data that are readily interpretable. But the weakness of interactions between nuclear magnetic moments and their environment also makes NMR signals weak, through small spin polarizations and small voltages induced in the coils of our NMR probes.

The battle against low sensitivity has been waged since the early days of NMR. One of the principal weapons has been indirect detection, which is the concept of using NMR signals from one set of nuclei, whose signals are relatively strong, to “announce” the NMR properties (e.g., frequencies, couplings, relaxation rates) of another set of nuclei, whose signals are significantly weaker due to their smaller magnetic moments or lower abundance. This concept arose long before I began doing magnetic resonance myself, in fact before I was born, so my understanding of its origins is certainly incomplete. Nonetheless, my understanding is that the first demonstration of effects that resemble indirect detection in NMR appeared in a paper by Bloembergen and Sorokin in 1958 [1]. This paper showed that ^{133}Cs NMR signals from solid CsBr could be excited by applying a radio-frequency field at the ^{133}Cs NMR frequency while simultaneously applying a second, weak radio-frequency field either slightly above or slightly below the ^{81}Br NMR frequency, with a detuning matched to the strength of the ^{133}Cs field. Thus, in principle, the ^{81}Br resonance condition could be detected through its effect on the ^{133}Cs NMR signal. Perhaps more famously, and with the explicit goal of enhancing NMR sensitivity, the 1962 paper by Hartmann and Hahn [2] explained how the NMR frequencies of rare nuclei in solids can be detected through a

diminution of signals from abundant nuclei, after spin-locking the abundant nuclei and irradiating the rare nuclei under “Hartmann-Hahn” matching conditions.

Although the concept of indirect detection began in solid state NMR, the emphasis shifted to liquid state NMR when modern multidimensional techniques, with spin polarization transfers driven by scalar couplings, began to take shape. Early experiments by Maudsley and Ernst [3] and by Bodenhausen and Ruben [4] laid the groundwork, showing that two-dimensional ^1H - ^{13}C and ^1H - ^{15}N spectra of molecules in solution should be recorded (in most cases) by detecting the ^1H NMR signals, letting the ^{13}C or ^{15}N frequencies express themselves in the indirect dimension.

While indirect detection (i.e., ^1H detection) came to dominate NMR spectroscopy of organic and biological solutions, many years went by before analogous experiments in NMR spectroscopy of organic and biological solids were reported [5, 6]. The problem was that ^1H NMR lines of organic and biological solids are inherently broad, typically ~50 kHz in width due to strong ^1H - ^1H dipole-dipole couplings. The large ^1H NMR linewidths nullified any sensitivity advantages of ^1H detection that would otherwise accrue from the larger magnetic moments of ^1H nuclei. But as accessible magic-angle spinning (MAS) frequencies began to exceed 30 kHz, due to progress in MAS technology [7], it became possible to attenuate the ^1H - ^1H couplings to the point where ^1H detection became advantageous, simply by spinning the sample rapidly. Additionally, ^1H - ^1H couplings could be attenuated by partial deuteration [8, 9].

With MAS frequencies now surpassing 100 kHz, indirect detection is becoming the preferred approach in many solid state NMR labs, greatly reducing the requirements for sample quantities and measurement times, and also providing new information through well-resolved ^1H NMR chemical shifts, ^1H - ^1H distance restraints in structural studies, and other parameters. This Virtual Special Issue contains a collection of articles from past issues of the *Journal of Magnetic Resonance*, each describing significant contributions to methodology for indirect detection in solid state NMR. In addition, the three articles by Ishii, Veglia, Lange, and their coworkers, which were written specifically for this issue, describe new developments and current directions.

While it is clear that indirect detection methods have become an essential component of modern solid state NMR, important questions remain to be addressed. These include: How rapidly can one spin a sample? At what point do limitations on sample volumes at higher MAS frequencies outweigh the potential gains in sensitivity from sharper ^1H lines? Which classes of samples and scientific problems benefit most from ^1H detection? What are the best ways to obtain signal assignments and structural restraints in ^1H detection experiments? Are new types of pulse sequences possible, helpful, or necessary? Which isotopic labeling schemes are most useful? Will ^{14}N and ^{17}O signals become important? Can ^1H detection at high MAS frequencies be combined with hyperpolarization? Answers to these and related questions will undoubtedly appear in the near future, most likely in the pages of this journal.

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