Signal Detection in NMR: Macroscopic, Microscopic, and Nanoscale

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Synopsis

Practitioners of biomedical NMR-- while diversified in their backgrounds and interests-- face nonetheless one problem in common: the inherent weakness of the NMR signal. This limits our spatial resolution, or more simply, the number of spins we can detect. We therefore pose the questions: what are the current limits of detection, and how may they be extended? Several methods are discussed, including the polarization transfer in noble gases and of Carbon-13, which promise improvements in Signal to Noise Ratio of factors approaching 10,000, and open the way for new and unsuspected applications

Practitioners of biomedical NMR-- while diversified in their backgrounds and interests-- face nonetheless one problem in common: the inherent weakness of the NMR signal. In our society, with its emphasis on imaging and localization, this translates into the quest for ever finer spatial resolution, or in more elemental terms, for the detection of ever smaller numbers of spins. One is then led to ask: is there a fundamental detection limit, never to be transgressed? The answer, I hope to demonstrate, is no -- but that there are instead provisional limits, which may be approached, over even overcome, by increasingly ingenious experimental methods, operating at a nexus of physics, chemistry, and biology. The results to date augur for new horizons of progress, unimagined even a decade ago.

We begin with the basic facts of signal formation: the alignment (i.e. polarization) of nuclear spins in a magnetic field, and the conversion by a transducer (or probe) of spin energy, in the form of quanta (or photons) into an electric current, which our scanner will detect, transform, and display. The polarization of a specimen is determined by the numbers of spins, denoted n_w and n_a, having their magnetic moments aligned with or against the polarizing field -- where $n_w + n_a$ is the total spin population n_{tot} , and $n_w - n_a$ is excess number of spins δn aligned with (i.e. parallel to) the field. Then $\delta n / n_{tot}$ is called the fractional polarization. The observable NMR signal is proportional to this; and we will later see how to enhance the signal, by driving the fractional polarization beyond its normal equilibrium value.

Each detected spin gives up its energy in the form of a photon which is captured by the transducer; but because of thermal agitation, the transducer inevitably adds a certain irreducible amount of electrical noise, depending on temperature. Our commonest measure of *detectability* is then the Signal to Noise ratio (SNR) --usually written (*1*) as the square root of the ratio of detected signal and noise energies , i.e. as $\bullet(E/kT)$, where E is the signal energy in a given voxel (or spectral point), and kT is the Boltzmann constant times the absolute temperature. We then define , for any fixed temperature T, the *threshold of detectability* to be SNR = 1, and ask what is required to reach it.

Now the energy per quantum (or photon, as we shall say) is Planck's constant h times the frequency ν, so that the ratio $h\nu/kT$ is just the squared SNR per received photon– typically a small number in NMR, specifically 2×10^{-5} for protons in a field of 3.0 tesla at room temperature (300°K). We then ask what is the threshold number of photons n_t to achieve SNR = 1, i.e. $\bullet(n_t h\nu/kT) = 1$; the answer is obviously $n_t = kT/h\nu$, or about 5×10^4 in our example. We show in the appendix that at the minimum, a sample of $\sim 5 \times 10^9$ spins is required to generate this number of photons. For water protons, this corresponds to a volume of $\sim 7.5 \times 10^{-17}$ litre, or a cubic voxel 0.4 micron on a side.

The failure to achieve such spectacular resolution is essentially the failure to capture all the available photons in a timely manner; that is, the transducer efficiency (defined by Hoult-Richards (*2*) as the oscillatory magnetic field strength, per square root of power P absorbed by the probe) is too low. For example, with a realistic head coil operating at 3.0 tesla and room temperature, we calculate that 1.2×10^{18} water protons are needed to achieve SNR = 1 in a single free induction decay. This represents a volume of about 20 nl, i.e. a cubic voxel 270 microns on a side, which is 2.4×10^8 times greater than the threshold sample size, as determined above, from purely physical constraints .

What then can be done to improve the SNR and advance towards the detection threshold? Broadly speaking, there are two paths: to increase the fractional polarization beyond its equilibrium value, or to improve the transducer efficiency (from which we do *not* exclude cooling the transducer, although this actually moves the threshold , in addition to raising SNR). Many methods have been tried and the following list is not exhaustive : i) polarization transfer: including cross-relaxation via the Overhauser effect and Dynamic Nuclear Polarization (DNP) in solids and liquids, hyperpolarization of noble gases, coherent manipulation of spin dynamics e.g. INEPT and Hartmann Hahn matching, etc. (*3*) ii) reduction in the size of the transducer --surface coils, micro-coils and NMR microscopy (*4*) iii) lowering the noise temperature of the transducer --including superconducting and cold-copper probes (*5*) (iv) increasing the detection photon energy i.e. by double resonance (*6*) (v) exploring highly efficient non-inductive transducers: the Superconducting QUuantum Interference Device (SQUID), and Magnetic Resonance Force Microscopy (MRFM) (*7*) (vi) chemical reduction of olefins with molecular para-hydrogen (*8*) . The current state of the art is indicated by the observation of the equivalent of 1×10^{12} water protons at room temperature in a field of 14 T (*4d*), and the achievment (at millikelvin temperatures) of the equivalent sensitivity of 2 or 3 electron spins by force microscopy (D. Rugar, personal communication).

We shall confine subsequent discussion to two of the most applicable methods – hyperpolarization of rare gases, and dynamic nuclear polarization – which share several features, and are thus amenable to co-discussion, despite the fact that the former is typically performed in vapor phase, the latter in condensed phases. Both methods achieve polarization transfer by cross-relaxation from an electron spin to a nuclear spin: for example, between the valence electrons of rubidium vapor and the Xe nucleus, or between a stable free radical and the ^{13}C nucleus. In both instances the transfer is driven (pumped) by applying radiation (optical or microwave) to manipulate the populations of the electron spin states. In both, the interaction energy between the active electron and nucleus contains a term of the form:

$$\hat{H} = A\{\hat{I}_z \hat{S}_z + \tfrac{1}{2}(\hat{I}_+ \hat{S}_- + \hat{I}_- \hat{S}_+)\}$$

where the circumflex denotes a quantum mechanical operator, and A is a numerical factor. The I's pertain the nuclear spin, the S's to the electron spin. The quantities are of particular interest and have a conceptually transparent meaning even for the non-physicist. The plus and minus subscripts denote so called "ladder operators" (ascending +, descending -) which perform the function of flipping the orientation of a spin with respect to the polarizing magnetic field. That is, a "+" operator flips an anti-parallel spin into the parallel orientation; a "-" operator does the converse. A product of the two operators (such as we have written) performs a "flip flop" operation on a spin pair having opposite orientations; that is, a state with nuclear spin parallel and electron anti-parallel is converted to a state with nuclear spin anti-parallel and electron parallel, etc. These concerted processes of the two spins allow the exchange of energy and polarization, which are governed by rate equations reminiscent of those employed in chemical kinetics. The following analogy, drawn from the mass action law, is illuminating, although inexact. Polarization transfer resembles a chemical reaction, for example, the alkaline hydrolysis of an amide in aqueous solution, which can be driven past its usual completion point by removing the volatile ammonia from the system (say by a vacuum pump). The application of microwave or optical radiation to the two-spin (electron-proton) system plays (in this analogy) the role of pumping, and drives the cross-relaxation to a point not otherwise attainable. The consequences can be spectacular – including SNR gains of up to 10^4 (or 80 dB), as will be illustrated by the subsequent papers in this session.

Appendix:

The population ratio n_w/n_a at thermal equilibrium is $\exp(h\nu/kT) \bullet 1 + h\nu/kT$, for $h\nu/kT \ll 1$, from which the fractional polarization: $\delta n / n_{tot} = (n_w / n_a - 1)/(n_w / n_a + 1) \bullet h\nu/2kT$. Then the threshold number of photons is $n_t = kT/h\nu$; and assuming perfect photon capture gives $n_t = \delta n$, from which $n_{tot} = 2(kT/h\nu)^2$. From the efficiency F we get the signal power $P_s = \{\omega V M_0 F\}^2/4$ where ω is the angular frequency, M_0 is the magnetization for and V is sample volume which enables calculation of the SNR with $F = 9 \times 10^{-7}$ for a reasonable volume head coil operating at 128 MHz.

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