

Symphony of Silent Spins

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Have you ever been stuck in a traffic jam on a June afternoon in Lahore? You are at the head of the lane and the traffic light is red. You are listening to your prospective employer on the cell phone who is trying to negotiate a lucrative offer, but the cellular company is known for its poor signal coverage and you are having difficulty in making sense of the conversation. All of a sudden there is a cacophony of horns and loud discouraging shots, reminding you that the lights have, in fact, switched colour. Your employer's speech virtually turns into a murmur dying out in the auditory tumult of the environment.

Observing nuclear spins in a magnetic resonance experiment is much like listening to the murmurs of your employer against the huge roar of horns and traffic.

Many of us enjoying the luxuries of urban residences have more or less undergone or know of someone who has undergone an MRI scan. The abbreviation stands for 'magnetic resonance imaging'. The scan is simply a snapshot of nuclear spins placed in a strong magnet, and the spins are emanating, not sound, but electromagnetic radiation. The radiation lies in the hundreds of Megahertz range and can be picked up with a properly designed radio that has been tuned to receive such high radio-frequencies. Strictly speaking the radiation emitted comprises several frequencies which are characteristic of the kinds of spins present and their environment inside the molecule. By looking at an imprint of the frequencies, it is possible to make intelligent guesses of the molecule's internal structure. But the intrinsic problem with MRI is its low sensitivity—the signal originating from a nuclear spin is very weak. In

the context of my analogy of the traffic jam, the signal is hardly audible and is imbedded in a loud and mainly random clutter of background noise. In fact, present day technology falls short of making sense of the radiation from a *single* nuclear spin, it is simply too weak to be untangled from the noise. What then, makes an MRI scan possible?

To answer this question and to tackle the problem of insensitivity, one needs a foray into 'quantum statistical mechanics': quantum mechanics, one of physics' most powerful theories applied to a collection of a large number of particles, in our case nuclei.

A select class of nuclei such as ^1H , ^{13}C , ^{15}N , ^{31}P and ^{19}F possess a property called the 'spin'. Like many quantum properties, the spin is difficult to interpret but its manifestations are evident. The spin translates into the nuclei behaving as tiny magnets, tiny indeed, about 10^{27} or a billion billion billion times smaller than the magnet inside your cell phone loudspeaker. Furthermore, in a liquid, these tiny magnets, attached to molecules, are whimsically re-orienting in all random directions. The net effect is, therefore, that the liquid sample is unmagnetized.

However, we can place the sample inside another very strong magnet, stronger than most of us have ever experienced in our lifetimes. In the presence of this extra magnet, the spin magnets tend to line up parallel or anti-parallel to the direction of the field. Just imagine a disorganized jamboree of scouts (spins) being brought into order by the admonition of a strict scoutmaster (the external field).

The parallel and anti-parallel directions may

be called the ‘up’ and ‘down’ states. The spin has lower energy when it is in the up state resulting in a very minute excess of spins in one state over the other. I must reiterate, this excess is minute. In typical conditions, for 500,000 down spins there will exist 500,001 up spins, the *fractional* population difference being only one in a million. But no matter how small it is, this net excess *must* exist to produce an MRI signal.

An excess of a single spin is insufficient to elicit a detectable signal, but if we have a bigger volume of sample and hence a large number of excess spins, we can easily cross the detection threshold. This is the situation when the spins are all acting additively and contributing to the strength of the signal. The individual spins are not louder, we just have more of them. I believe this is the simplest solution to low sensitivity and at first sight, should always work.

However, the picture I have painted is not all that simple. The up and down states are separated by an energy gap. Temperature is providing the spins with energy kicks strong enough to make them step over the gap and fluctuate between the two orthogonal states. Consequently, this temperature-dependent energy tries to randomize the spins and counteract the effect of the applied magnetic field. The result is an ongoing competition between magnetic ordering and thermal disordering. At the end, some sort of compromise is reached and the spins find themselves happy with a fractional population difference that is determined by two factors, the temperature and the size of the energy gap. The mathematical details of this compromise were in fact spelled out by the Austrian physicist Ludwig Boltzmann even before the quantum theory was born. The Boltzmann rule is in fact a trap for conventional MRI, it prevents build-up of polarization and muffles the orchestra of spins.

Apparently, the population difference (also called the polarization for obvious reasons) can be enhanced by lowering the tempera-

ture and making the spins less agitated; or by increasing the applied field and widening the energy gap which thereby becomes more difficult to cross.

How far can these approaches take us? I am afraid, not too far. In a conventional magnetic image of the human tissue, we are rescued by the profusely large number of spins, namely hydrogen nuclei or protons, thanks to the abundant water, protein and lipid contents of these tissues. However, nature is not always so generous and many important chemicals only exist in trace amounts. Ever thought of the neurotransmitters serotonin and dopamine which control our innate feelings of excitement and fear, anguish and delight, love and rage? These signalling chemicals, vital they may be, come in exceedingly small concentrations and the MRI signal they produce will be dauntingly small. Furthermore, it is not possible to artificially increase their concentration in the naturally available setting.

Let us now look at the second option, lowering the temperature and trying to freeze the spins, locking them in the up state. But this approach has its own problems. The energy gap is so small that even very cold temperatures can randomize the spins. So for achieving significant polarizations, one has to move down not just to the cold, but to the *extremely* cold, for example, 260 degrees below freezing! This is even colder than the surface of the planet Pluto. These temperatures are surely achievable but impractical for most cases of interest. Quite obviously, the human subject cannot be subject to such inhuman temperature zones and for non-medical applications too, most liquids will freeze well above this temperature.

The third option for increasing the spin polarization is to increase the magnetic field. This time, we are limited by technology. The strong magnet in an MRI experiment is both similar and different to the solenoid magnet we are accustomed to, for example, in our doorbells. The magnetic field is produced

by passing current through a coil of wire, as in the doorbell solenoid, but the material used is not copper but a superconducting alloy of niobium and tin. The zero resistance of the material allows the coil to carry an exuberant amount of current and that too without a power source or dissipation of heat. The large current produces intense magnetic fields, between 1 and 20 Teslas. For comparison, a strong permanent magnet (the one you see clinging to your refrigerator) has a strength of only about half a Tesla and the earth's field is still 10,000 times smaller. However, there are technological limits to the maximum field achievable: we are limited by the maximum current the alloy can carry without losing its superconducting properties and structural stability. The current record is above a Kilo Tesla in an explosive underground, quarantined experiment, where neither the magnet nor the sample survived. Safer experiments set the current limit to only 20 about Teslas where the enhancement in spin polarization is insignificant. Furthermore, one of the very reasons why MRI is so rarely administered in many developing countries is the cost, it is always expensive buying and maintaining a superconducting magnet.

At the outset, the situation does not look promising and it appears that we cannot make the nuclear spins ring louder, the burden of observation lies on us, we have to be more attentive. Also then whither our hopes of observing trace metabolites with reasonable accuracy and resolution. Deadlock?

However, the antidote to many a poison lies in the poison itself. Ironically, quantum statistical mechanics also presents one way to overcome the polarization problem it had created in the first place. The key is not to fall into the Boltzmann trap.

The hydrogen nucleus is the most frequently observed species in MRI. This is partly because of its relative preponderance in water and human tissue. But even though it gives the strongest signal amongst the family of

magnetic resonance active nuclei, yet its polarization is devilishly small, one in a million, as I previously mentioned. So if we can think of a way of by-passing the Boltzmann distribution of spins in hydrogen, we are likely to gain a huge advantage.

The hydrogen molecule, comprising two nuclei, is deceptively simple but the magic of quantum mechanics turns even this object into a highly interesting affair. The pair of spins when placed in an external field, can exist in four states: up-up, down-down, up-down and down-up or their linear combinations. Similar to the case of a single spin, these four states have different energies but the distribution is not solely governed by Boltzmann rules. There is another simple but far-reaching rule operative in the quantum statistical world: the 'Pauli principle'. The principle at the one hand, explains the formation of black holes and neutron stars and at the other, describes when and how hydrogen atoms can come close together and recombine in making something as simple as a hydrogen molecule.

In simple words, the Pauli principle states that particles can recombine only when the resulting *molecule* obeys certain symmetry considerations. Now the molecule is not just the spin of the nuclei, it also comprises the spins of the electrons and the translation, vibration and rotation of the molecule as a whole. Each of these properties is called a 'degree of freedom'. Every degree of freedom possesses its own symmetry and in the molecule, the components must combine to impart the whole molecule with a particular symmetry. A simple example from arithmetics can elucidate my point. Suppose we have two variables x and y and would like their product to be negative, that is, to possess odd symmetry. Clearly, an odd (or negative) x must combine with an even (or positive) y and an even x must combine with an odd y . Like combinations such as both variables being odd and both being even are not permitted. Conversely, if y is even, we can *always be sure* that x must be negative.

In other words, we have forced x to take up a certain state *dependent* on y . The degrees of freedom become correlated. Likewise, in the hydrogen molecule, we can force all the nuclei to exist in just one state if we can choose the other degrees of freedom. The energy gaps in the nuclear spins are very small and extremely difficult to manipulate, but the gaps in the molecular motion are very large and it is easy to redistribute molecules in one level or the other. This fact helps us choose the correct molecular degree of freedom and the Pauli principle ensures that all nuclear spins are in the same state. Perfectly polarized! All of them lined up in the up-down state.

With ‘hyperpolarization’, we have now entered a new paradigm of MRI. Hydrogen nuclei can now be polarized with a fraction of one in one, rather than one in million, about a million-fold improvement. The Boltzmann trap is carefully by-passed.

The hydrogen prepared in this special way, called ‘*para*-hydrogen’ can arguably pave the way for a radically new outlook in MRI and spectroscopy. In MRI, we can possibly acquire higher contrast, sharper images and in spectroscopy, we can now shed light onto the dark areas and see the otherwise hidden trace metabolites.

The lung tissue, for example, has very poor hydrogen content. In an MRI scan a piece of lung will be almost invisible. However, air mixed with *para*-hydrogen can be inhaled and the tissue simply “glows up” enabling detailed scans. It is also possible to measure the rate at which the gas moves through blood and how different tissues in the brain take up this gas, or possibly how heart tissue behaves in congestive heart failure.

Furthermore, we are not only limited with hydrogen. The hyperpolarization can also be transferred to other nuclei such as carbon and phosphorus, enabling highly revealing and sensitive non-hydrogen MRI scans. The options are quite limitless enabling us to ask questions we have never been bold enough to

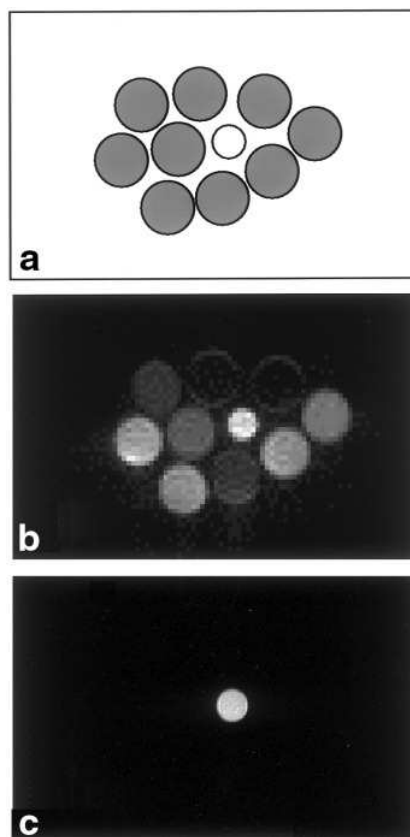


Figure 1: Image from normal and *para*-hydrogen test tubes. (a) is the phantom with the hyperpolarized sample represented by white, (b) and (c) represent images taken in different conditions. The contrast in (b) is evident and (c) shows that only the test tube containing the *para*-hydrogen shows up. (Image reproduced from K. Golman *et al.*, *Magn. Reson. Medicine* **46**, 1 (2001).)

ask before. For example, could this, as yet unexplored avenue in hyperpolarized functional magnetic resonance open up new vistas for investigating the very metabolic foundations for our thought and consciousness? Could this illuminate the biochemical basis of disease and suggest intelligent therapies? Can our perfect polarizations even absolve us from the need for using expensive and bulky superconducting magnets, bringing MRI within the reach of the common man.

After all, the silent spins are silent no more, so listen to their symphony for hearing is believing!