Laser-polarized Noble Gases for Magnetic Resonance Imaging

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Abstract. This paper describes a technique in which noble gases such as $^3$He and $^{129}$Xe are polarized using optical pumping techniques, and used as a source of signal for magnetic resonance imaging. Techniques for polarizing the gas and a few representative examples of clinical applications are presented. Also emphasized is the connection between noble-gas imaging and the use of polarized gaseous targets in nuclear and particle physics experiments such as E142, an experiment at SLAC to study the spin structure of the neutron.

INTRODUCTION

Noble-gas imaging is a new type of magnetic resonance imaging (MRI) that utilizes laser-polarized noble gases. The noble gas, typically $^3$He or $^{129}$Xe, is polarized using optical pumping techniques. It is subsequently inhaled by the subject, and an MRI scanner, tuned to the Larmor frequency of the noble gas nucleus, is used to make an image. The result is unprecedented resolution of the gas space of the lungs. In the case of $^{129}$Xe, the gas is also absorbed into the blood and transported throughout the body. Imaging of the brain and other parts of the body have also been demonstrated.

There are now two established techniques for polarizing large quantities of noble gases. One approach, known as spin-exchange optical pumping, involves the optical pumping of alkali-metal atoms such as rubidium (Rb) and potassium (K) and subsequent spin-exchange collisions with noble-gas atoms [1]. Another approach, known as metastability exchange, involves the direct optical pumping of helium (He) in a metastable $^3S_1$ state, and subsequent collisions in which polarization is transferred to ground state atoms [2, 3]. While both polarization techniques were demonstrated in the 1960’s, a great deal of basic research[4] and the evolution of laser technology have played a key role in making them practical.

Noble-gas imaging was first proposed by G. Cates and W. Happer at Princeton and M. Albert at Stony Brook in 1993. The first images, of the gas space of the excised lungs of a mouse, were published in Nature in 1994 [5]. Images of the gas space of human lungs followed shortly thereafter, and were made by both a Princeton/Duke collaboration in the US [6] and a Mainz/Heidelberg/Ecole Normale Superieure collaboration in Europe [7]. Both collaborations drew on experience gained in building large polarized $^3$He targets. In the US, in 1992, a polarized $^3$He target, based on spin-exchange optical pumping was used at SLAC (E142) for the study of the spin structure functions of the neutron [8, 9]. Shortly thereafter another polarized $^3$He target, based on metastability exchange, was used at Mainz to measure the electric form factor of the neutron [10]. In both cases the
amount of gas involved was on the order of a quantity corresponding to a liter at STP, thus establishing a necessary requirement for noble-gas imaging, and setting the stage for medical applications.

Noble gas imaging is an excellent example of an unexpected technological spin-off resulting from otherwise basic research. From its beginnings in 1960, a great deal of atomic physics research has been done on spin-exchange optical pumping. The same is also true of metastability exchange. The nuclear and particle physics communities have also badly needed targets rich in polarized neutrons, stimulating the development of techniques for producing large quantities of polarized $^{3}\text{He}$. While none of this activity was conducted in anticipation of an application in medical imaging, it is clearly the case that this new type of MRI would not otherwise have come into being.

POLARIZING GAS AND POLARIZED TARGETS

Spin-exchange optical pumping

Spin-exchange optical pumping is a two step process in which 1) an alkali metal such as Rb or K is optically pumped and 2) the nuclei of a noble gas such as $^{3}\text{He}$ or $^{129}\text{Xe}$ is polarized in subsequent spin-exchange collisions. For reasons that will be explained more below, the approach is often quite different depending on whether it is $^{3}\text{He}$ or $^{129}\text{Xe}$ that is being polarized.

For the case of $^{3}\text{He}$, the gas is typically polarized in a glass cell containing up to 10 atmospheres of $^{3}\text{He}$, around 70 Torr of nitrogen ($\text{N}_2$), and on the order of 10-100 milligrams of rubidium metal. The density of Rb vapor is controlled by heating the cell. The cell is irradiated with circularly polarized light with a wavelength of 795 nm, which corresponds to the $D_1$ transition between the $5^2 S_{1/2}$ ground state and the $5^2 P_{1/2}$ first excited state. The $N_2$ is included in the cell to induce “radiationless quenching” of the excited Rb atoms. Once the Rb atoms are polarized, polarization is transferred to the $^{3}\text{He}$ through spin-exchange collisions. The interaction responsible is a hyperfine interaction between the valence electron of the Rb atoms and the spin of the $^{3}\text{He}$ nuclei.

In order to maintain high Rb polarization, it is essential that the photon absorption rate per Rb atom be greatly in excess of the electronic relaxation rate. In equilibrium, the photon absorption rate is given by

$$\text{Photon absorption rate} = \gamma_{sd} [\text{Rb}] V P_{\text{Rb}}$$

where $\gamma_{sd}$ is the electronic relaxation rate, $[\text{Rb}]$ is the number density of Rb, $V$ is the volume of Rb vapor, and $P_{\text{Rb}}$ is the Rb polarization. If we assume that the Rb number density is set by other factors, eqn. (1) sets a requirement on the required laser power. Conceptually, enough laser power is required to replace the angular momentum lost to electronic spin relaxation.

Another critical factor in achieving high $^{3}\text{He}$ polarization is ensuring that the Rb-$^{3}\text{He}$ spin-exchange rate is greatly in excess of $^{3}\text{He}$ spin-relaxation rates unrelated to spin...
exchange. The time evolution of a sample of $^3$He is given by

$$P_{\text{He}}(t) = P_{\text{Rb}} \left(1 - e^{(\gamma_{se} + \Gamma)t}\right) \frac{\gamma_{se}}{\gamma_{se} + \Gamma}$$

(2)

where $P_{\text{He}}(t)$ is the time dependent nuclear polarization of the $^3$He, $\gamma_{se}$ is the Rb-$^3$He spin-exchange rate, and $\Gamma$ is the spin-relaxation rate due to all processes other than spin exchange. Under most circumstances, $\gamma_{se}^{-1}$ is somewhere between 5 and 20 hours. The value of $\Gamma^{-1}$, which is a number characteristic of each cell and a quantity often referred to as a cell’s lifetime, must be long compared to $\gamma_{se}^{-1}$ to achieve high polarization. A great deal of effort has gone into establishing techniques for achieving long values of $\Gamma^{-1}$ on a consistent basis.

Polarizing $^{129}$Xe has associated with it very different challenges than is the case when polarizing $^3$He. In particular, the electronic spin relaxation rate associated with 5-10 atmospheres of $^{129}$Xe is on the order of several thousand times faster than what one typically encounters when polarizing $^3$He. This makes it difficult to maintain high Rb polarization. One solution to this is to use a very dilute mixture, on the order of 1%, of Xe, with the remainder of the gas being mostly $^4$He or N$_2$ [11]. Such a mixture can still be used at relatively high pressures while maintaining a manageable electronic spin relaxation rate. The high pressures are desirable because they broaden the absorption line of the Rb, better matching the broad spectral output of the high-power diode lasers. The dilute mixture can be flowed through a polarization chamber quickly because Rb-$^{129}$Xe spin-exchange rates are much higher than is the case for Rb and $^3$He. The Xe can then be frozen out of the gas mixture and accumulated. There are certainly other approaches to polarizing $^{129}$Xe, and the options can be expected to become more numerous as better lasers are developed.

The E142 polarized $^3$He target

The development of target technology for experiments such as SLAC E142 played a critical role in both in inspiring and enabling noble-gas imaging. When E142 was proposed, spin-exchange experiments were typically performed in cells not unlike the small spherical cell shown in Fig. 1, with volumes of 10 cm$^3$ or less. Cells with volumes as large as 35 cm$^3$ were being developed for use at labs such as TRIUMF and Bates, but had not yet been demonstrated. The SLAC target cells, also shown in Fig. 1, had volumes of around 150 cm$^3$ in volume. The SLAC target, at the time it was proposed, represented more than an order of magnitude increase in the quantity being polarized than what had previously been achieved. It marked the first time that (at STP) liter-type quantities of $^3$He had been polarized, and presented the possibility for considering other applications that would require significant quantities of $^3$He. The SLAC target cells were comprised of two chambers, an upper “polarization chamber” in which spin exchange took place and a lower “target chamber” through which the electron beam passed.

As emphasized earlier, laser power is a limiting factor in determining the quantity of noble gas that can be polarized. When E142 took data, five titanium:sapphire lasers were used, each pumped by an argon ion laser. Collectively they produced 20-25 W.
Each of the five systems cost on the order of $100K and drew close to 50 kW out of the wall. Shortly after E142 took data, however, a solid-state technology became available known as fiber-coupled high-power diode laser arrays. In these devices each of a dozen or more emitters on a single chip are coupled to fiber optics that can be bundled to produce a bright source of light. The diode array systems have a much broader linewidth than Ti:sapphire systems, around 1000 GHz as opposed to roughly 30 GHz, but they are still quite effective for optical pumping of Rb. A system producing 20-30 W costs around $20-25K, and only draws a few hundred Watts from the wall. Diode laser systems played an important role in E154 (the follow-on experiment to E142) and are critical to medical imaging where large power consumptive lasers are completely impractical.

**Metastability exchange**

For the purposes of this paper I have focused on spin-exchange optical pumping, but it is also important to describe metastability exchange. The technique relies on producing helium atoms in the metastable $^2S_1$ state using an rf discharge, and optically pumping them using a transition to the $^2P_0$ ($\lambda = 1.08\mu$). The polarized metastables subsequently collide with other helium atoms in metastability exchange collisions, during which a significant amount of angular momentum is transferred to ground state atoms.

There are both advantages and disadvantages to metastability exchange over spin-exchange optical pumping. On the positive side, metastability exchange is more efficient than spin-exchange optical pumping in terms of the number of photons required to produce a polarized $^3$He nucleus. Also, the cross section for the metastability exchange collisions is quite large compared to the cross section for alkali-metal—noble-gas spin exchange, so the process proceeds much more rapidly. On the negative side, metastabili-
FIGURE 2. Shown are two images off the gas space of human lungs (from different subjects). At left is a traditional ventilation scan in which the subject inhales radioactive gas and an image is made using a gamma camera. At right is an MRI in which the signal source is inhaled nuclear-polarized $^3$He. Both images were made at UVa.

ity exchange only works for pressures on the order of one Torr. Thus, once the $^3$He is polarized, it must be compressed in order to reach pressures over an atmosphere. The apparatus for metastability exchange ends up being significantly more complex than is the case for spin-exchange optical pumping, but the performance of a well designed system can be impressive. At the time of this writing most noble-gas imaging in the United States is performed using spin-exchange optical pumping, and most noble-gas imaging in Europe is performed using metastability exchange.

**NOBLE-GAS IMAGING**

The rapid growth of noble-gas imaging is due in part to existing difficulties in lung imaging. The current state-of-the-art method for imaging the gas space of the lungs is a nuclear medicine technique known as a ventilation scan. The subject inhales a radioactive gas, and a “gamma camera” is used to image the gamma rays that emanate from the subject’s chest. An example of a ventilation scan is shown in Fig. 2 on the left. While the image certainly reveals larger features, the practical resolution is on the order of a centimeter. In contrast, the image on the right in Fig. 2 is an example of noble-gas imaging using $^3$He. The improvement in resolution is striking, with details on the order of a millimeter becoming visible.

**Polarizing gas in a clinical environment**

In the early experiments with noble-gas imaging, the apparatus used to polarize the gas was very much the sort of equipment that one would expect to find in a physics
FIGURE 3. Shown is the first prototype commercial noble-gas polarizer. Shown in the inset is the “polarization chamber”, used for polarizing $^3$He by spin exchange. The polarization chamber can be seen to be similar to the polarization chamber of the SLAC target cells shown in Fig. 1.

laboratory. Among the implications of this was that physicists were required to operate the equipment. While this was appropriate for early experiments, it is impractical for extensive clinical studies. Medical research generally involves substantial numbers of trials. Only by establishing repeatability can patterns be identified. This places demands, however, on the equipment that is being used to polarize the noble gases. Ideally one would like the apparatus to be easy to operate so a well-trained technician could handle the job. It also needs to be very reliable. Often the patients being imaged are in ill health, and cannot tolerate or would be unwilling to reschedule a procedure should technical difficulties prevent the noble gas from being ready for an image.

The apparatus pictured in Fig. 3 is a prototype of the first commercial noble-gas polarizer. It is built to produce batches of $^3$He on a repeated basis. It is self contained, the controls are accessible from the front of the machine, and it is relatively easy to operate. Subsequent versions of the device are even more compact and user friendly.

The connections between the prototype polarizer shown in Fig. 3 and the technology developed for SLAC E142 are many. As an example, the inset in Fig. 3 shows the polarization chamber in which $^3$He is polarized. It can be seen that the polarization chamber is nearly identical in structure to the polarization chamber used in the polarized $^3$He target for E142 as depicted in Fig. 1.

Finding a clinical niche

While noble-gas imaging clearly provides images of the gas space of the lungs that are dramatically improved over what was previously available, a great deal of clinical research is needed before it can be established as a new clinical tool. With a reliable
source of polarized gas, however, it becomes possible for physicians to conduct studies on a regular basis on a wide variety of pathologies. At UVa, over 300 studies have been performed on both healthy volunteers as well as patients suffering from a variety of conditions. A few representative examples are shown in Fig. 4.

A nice example of a new insight that has come from noble-gas imaging pertains to asthma. In Fig. 4, on the image labeled asthma, small dark areas are visible that are not present on a normal lung. Researchers at UVa, seeing such features, came to refer to them as ventilation defects. They were first seen in images of volunteers that believed themselves to be completely healthy, but turned out to have mild asthma. Noble-gas imaging had accidentally detected mild asthma in volunteers that were otherwise asymptomatic. Establishing a means to detect asthma even in its mildest form may have important consequences. There are studies that suggest that treating asthma when it is quite mild is a good strategy to prevent more serious disease later. Research at UVa has now established noble-gas imaging as a useful tool for studying asthma [12], and additional research is continuing with NIH funding.

Another application of noble-gas imaging is the visualization of the dynamic process of moving gas into and out of the lungs. Because the signal from polarized $^3$He is so large, it is possible to obtain images very quickly, making it possible to construct real-time movies of the breathing process. Dynamic imaging appears to be useful for patients who have received a single lung transplant. In patients in which no rejection is taking

FIGURE 4. Shown are several examples of pulmonary pathologies in contrast to a healthy volunteer.
place, dynamic imaging reveals that gas moves quickly and in larger quantities into the
grafted lung. The native lung, being in poor condition, receives less gas at a slower rate.
In patients suffering from bronchiolitis obliterans (rejection of the transplanted lung)
the native and transplanted lung move gas at similar rates and in similar quantities.
To a physician examining the patient using conventional techniques such as spirometry
(which measures volumes of exhaled gas), the condition is often not apparent until it is
too late to treat. Using anti-rejection drugs early on can greatly improve the patient’s
chances of recovery.

CONCLUDING REMARKS

It is not possible within the scope of this paper to do a thorough job reviewing all
the medical applications that are being explored using noble-gas imaging. There are
numerous groups in United States, in Europe, and Japan that are actively pursuing
research in noble-gas imaging, and I have essentially restricted myself to describing
a few of the activities at UVa. Still, I hope it is clear that particularly where pulmonary
function is concerned, noble-gas imaging is already having an important impact. More
exotic applications, such as dissolved-phase imaging using $^{129}$Xe have yet to prove
themselves, but may expand the range of applications even further.

I hope I have also made the point that noble-gas imaging grew in an unexpected
manner out of basic research in atomic and nuclear physics. This lesson, that basic
research can have important and unanticipated results, is a message worth carrying
beyond our immediate community so that public support of all research can remain
generous.

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