Polarized ^{13}C for Use with Magnetic Resonance Imaging

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Abstract

We have studied several potential candidate materials that could be used to enhance MRI images through the use of hyperpolarized ^{13}C nuclei. We have found two potentially useful host materials and have begun the work in determining the proper doping required for successful MRI implentation. This experiment has begun the process of finding a suitable material that can be used with MRI and has pointed out what the next step should be toward the ultimate goal of introducing a polarized ^{13}C sample into a patient.

Principles of Nuclear Polarization

This entire experiment is predicated on the property of nuclear spin polarization. It is the driving phenomenon behind the functioning of Magnetic Resonance Imaging (MRI) systems. An understanding of nuclear spin and spin alignment is fundamental.

The phenomenon of nuclear polarization is a fundamental consequence of nuclear spin. Little needs to be understood about spin in this context except to know that the nuclear spin (the spin of a hydrogen nucleus or a carbon-13 nucleus, for example) can either be aligned with an external magnetic field or anti-aligned. This alignment is possible because of the intrinsic magnetic moment of every nucleus. It is the magnetic moment that makes each spin act as a small magnet which is then capable of interacting with the external magnetic field. The polarization of a material is described as the difference between the number of spins aligned with the field and the number anti-aligned divided by the total number of spins. A negative polarization indicates that more spins are anti-aligned than are aligned. The following equation shows how polarization is defined (where $N^{\uparrow}$ is the number of aligned spins, $N^{\downarrow}$ is the number of anti-aligned spins, and P is polarization).

$$P = \frac{N^{\uparrow} - N^{\downarrow}}{N^{\uparrow} + N^{\downarrow}}$$

The natural polarization state of a given population of nuclei is dependent on the external magnetic field, the temperature, and the magnetic moment of the species in question. The higher the magnetic moment, the stronger the interaction between the nucleus and the external field, and therefore, the higher the polarization. If there is no magnetic field, there is no polarization. However, if the temperature is finite, and a magnetic field is present, there is always some polarization which depends on these factors. At lower temperatures or higher magnetic fields, this natural polarization increases. This is referred to as the thermal equilibrium polarization. Under our experimental conditions with a temperature of 1 or 2 Kelvin and a magnetic field of 5 Tesla the thermal equilibrium polarization of most materials is approximately 0.5%. However, at room temperature this number is reduced by several orders of magnitude. For example, at $1.5T$, the usual MRI magnetic field strength, and $300K$, room temperature, the thermal equilibrium polarization of the ^{13}C nucleus is 0.0012%. The relationship between the thermal equilibrium polarization and the factors above is as follows:

$$P = tanh\left(\frac{\mu B}{k_B T}\right)$$

where P is the polarization, μ is the magnetic moment, B is the magnetic field strength, k_B is Boltzmann's constant, and T is the temperature.

Principles of MRI and NMR

In its essence, Magnetic Resonance Imaging (MRI) is a very sophisticated version of Nuclear Magnetic Resonance (NMR) systems. NMR is a method by which we can experimentally measure nuclear polarization. This technique takes advantage of the fact that each nuclear

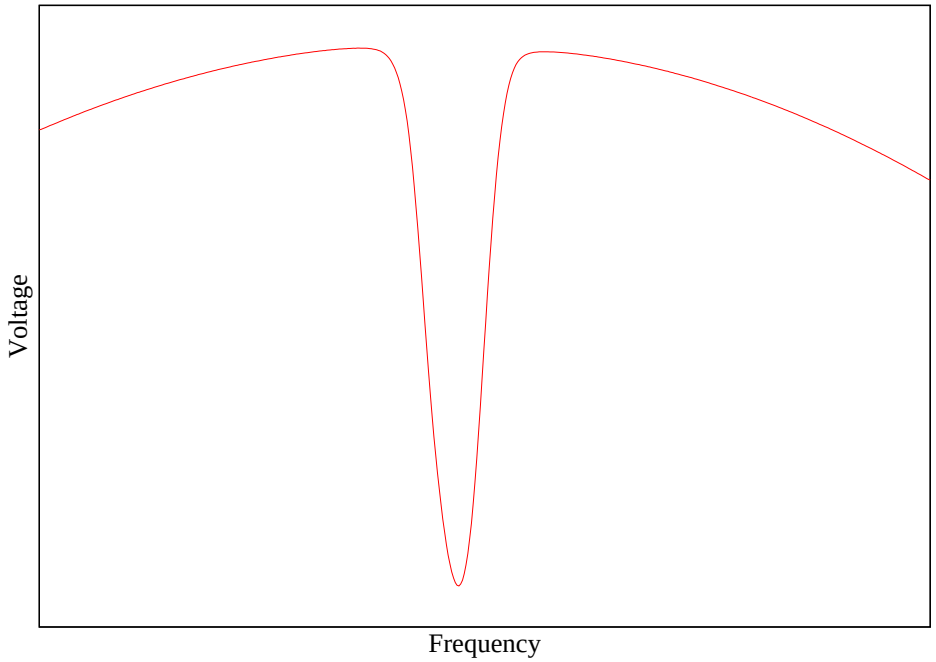

Figure 1: This is a positive hydrogen, or proton, signal.

species precesses about its axis (when placed in a magnetic field) at a specific frequency, the Larmor frequency, which depends on the external magnetic field. The material is thus placed in a known magnetic field. A series inductor–capacitor–resistor circuit (an LCR circuit) is set up with the material positioned around the inductor. The LCR circuit is tuned such that it resonates at the same frequency as the Larmor frequency of the nuclei in question. This tuning causes a voltage peak at the frequency which was chosen for resonance. This voltage response is commonly referred to as a Q curve. Now, when the LCR circuit's Q curve is measured on an oscilloscope, a power dip or peak can be seen that corresponds to the appropriate nuclei. This is because the nuclei are essentially sucking power from the circuit at the frequency (or giving power in the case of a peak). Figure 1 shows a positive polarization dip in an otherwise normal Q curve.

MRI systems use NMR to detect nuclear spins that are polarized and creates an image out of them. Most standard MRI techniques image the proton, or hydrogen nucleus. The patient is then placed in a strong magnetic field (around $1.5T$) and the thermal equilibrium signal that was discussed above is imaged. The imaging of the thermal equilibrium polarization is only possible because hydrogen is so plentiful in the human body (specifically, the hydrogen attached to the water molecule). Not surprisingly, different tissues have different concentrations of water and therefore show up in an MRI scan with contrast. NMR techniques show a stronger signal if the nuclei are more densely packed.

Principles of Dynamic Nuclear Polarization

Dynamic Nuclear Polarization (or DNP) is a process by which we can increase the polarization of a particular nucleus far beyond its thermal equilibrium polarization.

Environment

The environment in which we achieve this hyperpolarized state is extremely important. It requires a very high magnetic field of 5 Tesla as well as quite low temperatures around 1 Kelvin.

The field is created by a superconducting solenoid magnet. Inside this magnet is placed the coldest end of a helium-4 evaporation refrigerator. This refrigerator uses helium-4 which reaches its liquid state, at atmospheric pressure, at 4K. Large pumps create a low pressure situation in the atmosphere above the liquid pool. This removes the warm vapor allowing the liquid to reach temperatures of around 1K. Though it may not seem much, the difference of 3K at these temperatures can mean an order of magnitude or more difference in polarization.

Doping and the Physics of DNP

When we place a material under the conditions above, the thermal equilibrium polarization naturally increases. This increase, however, is nothing compared to the kind of polarization that can be achieved by DNP.

In order to polarize a material it must first have a source of free electrons. This is achieved by a process called doping. We add a chemical compound, that has a psuedo-free electron, to the material in small amounts. These free electrons are the electrons whose alignment is considered in the energy level diagram in figure 2.

The key ingredient that drives the polarization process is microwave radiation. We introduce microwaves of a specific frequency (and, therefore, energy) to the material. This will drive transition A or B in figure 2. Which transition is driven depends on the frequency of the microwave energy coming in. The frequency is directly related to the energy of the microwaves so it is clear how one frequency will cause the energy jump in A and a lower frequency will cause the lower energy jump indicated by transition B.

For polarization to occur, either states 1 and 3 or states 2 and 4 must be populated. This means that, to populate states 1 and 3 for example, we must empty states 2 and 4. Nuclei in state 2 can go to state 3 through microwave transition B. The electrons relax (meaning that they drop from the higher energy level to the lower one) much more quickly than the nuclei. When an electron relaxes, nuclei from state 4 go to 2 and those in state 3 go to 1. In this way, everything ends up in states 1 and 3. It is a much longer time (related to the relaxation time, a quantity that will be discussed later) before the nuclei relax (causing transitions from 4 to 3 and from 2 to 1) so these transitions do not need to be considered while microwave energy is present to drive the polarization.

Over time, as the nuclei relax,polarization is reduced. This can only occur when the driving microwave energy is not there to counteract the effects. This relaxation causes an

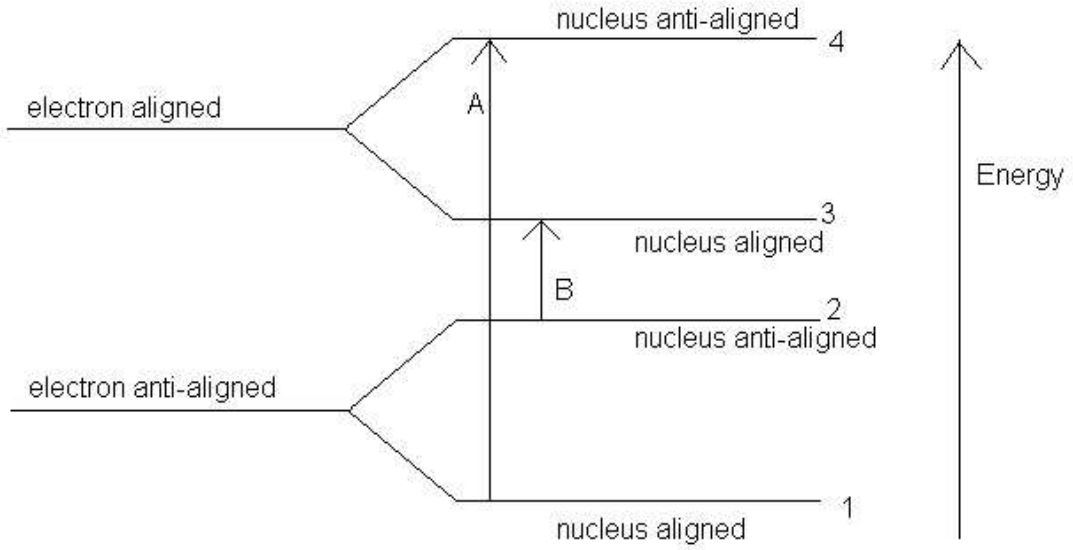

Figure 2: This is a general energy level diagram showing the relative energies of each possible spin orientation.

exponential decrease in polarization over time leading us to be able to determine a characteristic relaxation time which will be extremely important in this experiment.

NMR and Signal Analysis

NMR technology is used during polarization as well as in the MRI systems. During polarization the obvious question is raised: how do we measure the polarization? The answer is that we use NMR to detect the nuclear polarization as a dip in a Q curve as shown in figure 1. We subtract the Q curve from the total signal and are left with a signal such as the one in figure 3.

The area under the curve is linearly related to the percent of polarization. So, we are able to calculate a calibration constant that can take the area under the signal curve and translate that directly into a polarization.

Equal Spin Temperature

One of the major difficulties of this experiment, as we will see later, is that it is rather expensive to obtain the nuclei of interest. Specifically, we are interested in the more rare isotopes of naturally occurring nuclei such as carbon (the isotope being ^{13}C or ^{15}N). In order to get carbon-13 we would buy a material such as urea that has carbon in it and have the naturally occurring carbon-12 replaced with carbon-13.

While the possible benefits for MRI far outweigh the cost of a working material, we must experiment in order to find a material that is appropriate for our purposes (a selection

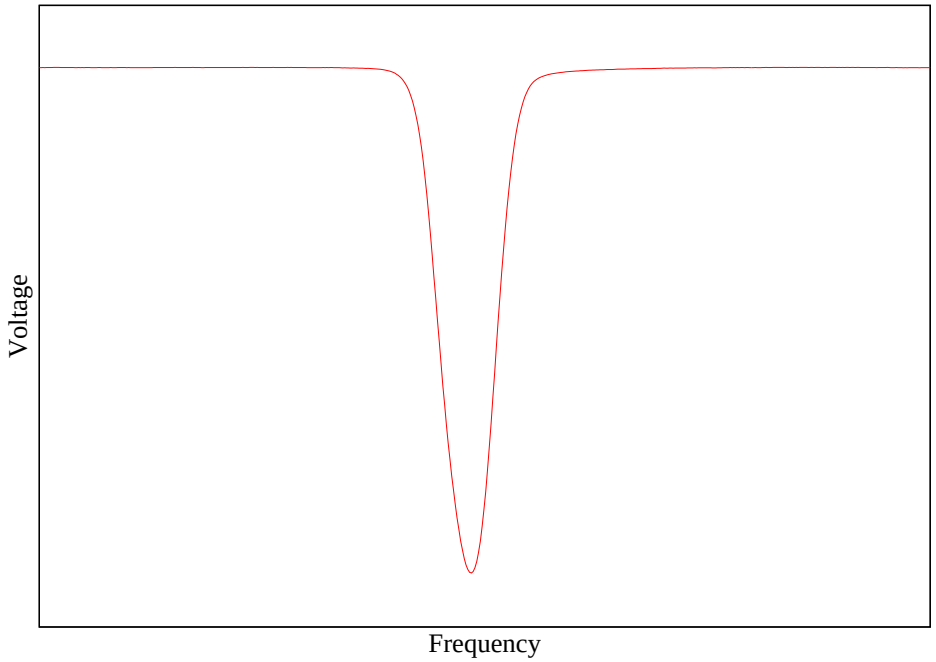

Figure 3: This is a subtracted proton signal.

process that will be discussed in more detail later). It is this experimentation that becomes a problem as it would require the purchase of many samples of expensive material that would ultimately prove ineffective for MRI use. There is, however, a way around this: a theoretical tool that is called equal spin temperature.

Basically, equal spin temperature allows us to know what the polarization of a ^{13}C nucleus would be if we know the hydrogen polarization from the same material (which works well as urea, and many other materials, have both hydrogen and carbon). In this way, we can buy inexpensive, unenhanced material and polarize the hydrogen. From this we can have a good idea how the carbon-13 would do without ever buying any.

The equation below relates total polarization to a nucleus' magnetic moment through an experimentally determined quantity called the spin temperature.

$$P = tanh\left(\frac{\mu B}{k_B T_s}\right)$$

Where T_s is the spin temperature. The spin temperature is the same as the actual temperature under thermal equilibrium conditions and only strays away as polarization is enhanced beyond the thermal equilibrium. So, if equal spin temperature applies (which appears to be the case in urea) then one can simply polarize the hydrogen to its maximum value, plug that into the equation and solve for T. Then we simply replace the magnetic moment of the proton with the magnetic moment of ^{13}C and plug in T to find P.

The Experiment

The purpose of this experiment is to ultimately be able to dramatically enhance the contrast of MRI images and to single out particular systems of the body.

MRI normally uses the thermal equilibrium polarization of an atom that occurs in great quantity in the body: hydrogen. Another option is to use nuclei that do not occur naturally in the body such as carbon-13 (actually, ^{13}C does occur naturally as approximately 1% of carbons are this isotope). These foreign nuclei are then introduced into the body at a higher polarization than the thermal equilibrium. Thus, the higher polarization makes up for any lack of quantity. In addition, the material can be made to target a particular system of the body. For example, the location of injection will help target an area but also different materials are handled differently by the body, metabolized at different rates and sent to different organs.

The polarization of the material and the lack of background noise (which would be caused by a high natural abundance in the body) would allow an extremely high contrast image of the organ or system in question to be produced by the MRI system. The advantages of this method are obvious. It could even help to resolve tissues that a standard MRI can not. The main consideration is that the nuclei relax rapidly at room temperatures. Therefore, the MRI must be performed with these time restraints taken into account.

Material Considerations

Because we polarize at such low temperatures and high magnetic fields it is important to consider that the polarized material will have to be warmed up and taken into a lower field in order to be used. This poses a severe problem as polarization is strongly temperature dependent. For this reason, it is important to achieve both a very high polarization as well as use a material with a long relaxation time. A high polarization is important because so much will be lost during warming that it must start out quite high to be useful at body temperature. The relaxation time is important because the material must be able to maintain its polarization during this time when there will be no polarizing microwave energy to drive the polarization. So, in our search for materials these are the two chief concerns.

Unfortunately, in any given material, higher polarization usually comes at the cost of shorter relaxation times. This is because a higher concentration of doping will generally allow a faster polarization but that same dopant that allows the polarization to soar when microwave energy is applied will speed along the relaxation when said energy is removed. So, there is a trade off when deciding how much dopant to use.

Another consideration which must be addressed before this experiment can move to the next stage is the safety of materials. Our primary choices for host materials (urea and glucose) are unlikely to cause problems but our dopant, Tempo, is a complex molecule that acts as an oxidant and warrants closer inspection. These considerations, however, are somewhat beyond the scope of this paper.

Data and Analysis

We considered several host material / dopant combinations that failed due to either poor polarization or fast relaxation time or both before we found promising material. Some of these failed materials include glucose with an iron compound as a dopant as well as glucose with Tempo (which failed ultimately because the Tempo was not uniformly dispersed, a problem that was later remedied).

The table in figure 4 shows the viable materials. It indicates for each their maximum polarization (positive or negative), doping amount (all are doped with Tempo), and a relaxation time (along with the temperature at which the relaxation occurred).

This table encompasses a great deal of information. The important aspects are maximum polarization and relaxation time. We will treat these two aspects separately in order to properly understand both the meaning of the data as well as the overall usefulness of each material.

Maximum Polarization

For any given material (urea or glucose in this case) the maximum polarization achievable depends upon many factors. One of these factors is doping. This is the only factor that we have left variable within each material and so we will study the maximum polarization of each material as a function of dopant concentration.

It is obvious that we should compare the glucose to the glucose and the urea to the urea. However, a question remains as to whether we can compare between the different types of enhanced urea samples. During the discussion on equal spin temperature it was indicated that one could use an unenhanced sample to gauge what an enhanced sample would do. This assumes that the hydrogen nucleus in a sample with carbon-12 would polarize the same as the hydrogen from a carbon-13 sample. So, the logic follows that we can compare the hydrogen maximum polarizations between the carbon-13 urea and the normal carbon-12 urea.

The case of the deuterated urea is a slightly different one. Here it is not some other nucleus that we are replacing, but the hydrogen itself (being replaced with a deuteron, hydrogen-2). The only reason that we are able to see a normal hydrogen signal in this material at all (as the table in figure 4 indicates) is because not every hydrogen is replaced. So, there is a weak signal but a proper calibration of the system should still allow us to read the proton polarization. This indicates that we can also compare the deuterated material to the others.

Figure 5 shows graphs of doping versus polarization for the urea hydrogen and the glucose hydrogen (the only two samples that have more than one doping to plot). The urea graph in figure 5 shows a wide range of maximum polarizations for the $1.2 \times 10^{19} s/mL$. This is a result of all of the different enhancements used. Though in general, these enhancements should not do a great deal to change the remaining nuclei, there are (not surprisingly) subtle interactions that can have an effect. One such interaction is between the deuteron and other nuclei. While we are not interested in the deuteron itself as a candidate for MRI use the presence of the deuteron in a sample enhanced with carbon-13 could lengthen the relaxation time of the carbon. That is the reason for the deuterated sample among our trial materials. The fact that it causes a lengthened relaxation time also indicates that its presence would

Material	Nucleus	Doping	Max. Pol.	Relax Time	Temperature
Urea	Hydrogen	0.8*	1.5%	none	none
Urea	Hydrogen	1.0*	17.0%	280 min.	1.40 K
Urea	Hydrogen	1.2*	58.0%	162 min.	1.64 K
Urea	Hydrogen	1.3*	38.0%	331 min.	1.34 K
^{13}C Urea	Hydrogen	1.2*	44.0%	none	none
^{13}C Urea	^{13}C	1.2*	5.0%	475 min.	1.31 K
Deut. Urea	Hydrogen	1.2*	22.0%	206 min.	1.8 K
Deut. Urea	Hydrogen	1.3*	40.0%	324 min.	1.48 K
Deut. Urea	Deuteron	1.3*	15.0%	77 min.	1.78 K
Glucose	Hydrogen	$5mM$	15.0%**	439 min.	1.43 K
Glucose	Hydrogen	$20mM$	65.0%	234 min.	1.43 K

Figure 4: Materials and their pertinent information. The materials are dissolved in glycerin and water. * These dopings are $\times 10^{19}$ free electrons/mL. ** This was the maximum achieved polarization but it would likely have gone higher given more time.

slow the polarization which could be why the polarization of the hydrogen in that sample is so much lower than the other materials of the same doping (if a sample polarizes too slowly, taking many hours, it is not uncommon that we never reach its maximum polarization due to time constraints).

These graphs indicate that the 1.2 doping of the urea is optimal and that an intermediate doping of glucose could yield improved results. It should be noted that the 5mM sample of glucose did not achieve its maximum polarization due to the fact that it is extremely slow but it would not likely have gone higher than 25%. However, high polarizations are not the only goal of this experiment so now we will turn to relaxation times.

Relaxation Times

It is notoriously difficult to compare among different relaxation times because each is taken at a different temperature. The reason for the relaxations being taken at different temperatures is that it is diffcult toe maintain stable temperatures in our refrigerator over night. The temperature differences make this quantity, though arguably more important than ultimate maximum polarization, more difficult to analyze.

We will only analyze the relaxation data for the two highest dopings of urea because the two lower ones do not show enough promise to be considered based on their low polarizations. The lower doping of glucose is also inadequate as far as maximum polarization is concerned and will not be considered. The graph in figure 6 show relaxation times for the various nuclei concerned.

We can begin by examining the glucose data. The important thing to consider is the change of relaxation time with temperature. The 5mM sample seems to drop off very rapidly with temperature, which is not a good sign. If the relaxation time gets too small as temperature increases to room temperature, there will be no time to perform the MRI test on the patient. For example, if the relaxation time becomes less then 1 second at room temperature,

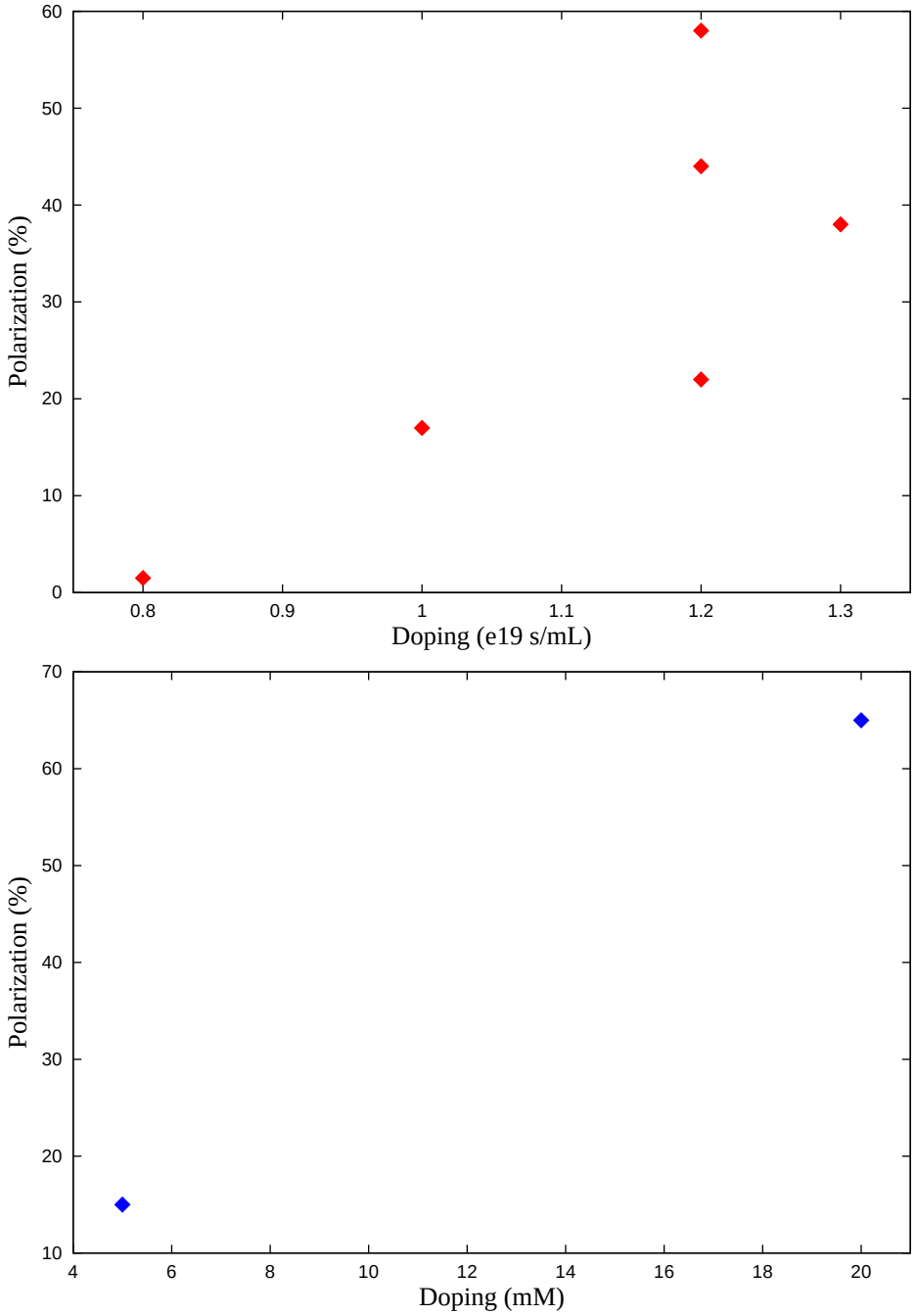

Figure 5: The first graph is urea hydrogen (both enhanced samples and unenhanced). The second is the glucose hydrogen.

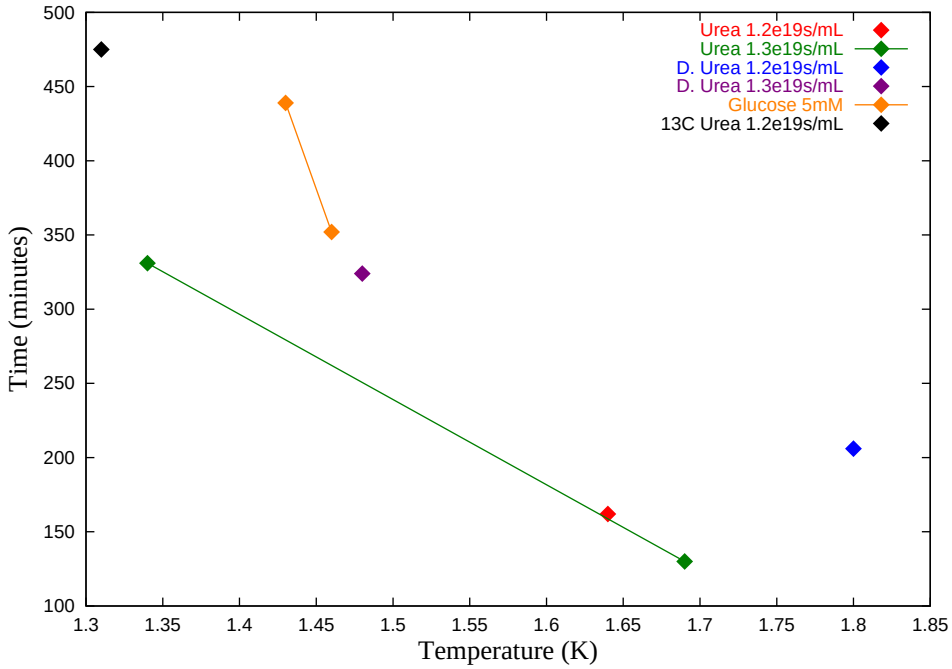

Figure 6: Relaxation times versus temperature. All of these times refer to the hydrogen nucleus except for the ^{13}C nucleus.

then most of the polarization will be gone within 1 second and there is not time to image the polarized nuclei.

Turning our attention to the regular urea samples we can see that they all fall in the same line. While we wouldn't expect this relationship to be linear, we can imagine that on these small temperature scales a linear approximation is not unrealistic. We can get a reasonable understanding of the relaxation time characteristics using these lines. The fact that all of the regular urea points fall on the same line indicates that one sample is not significantly different than the other with regards to relaxation time. Thus, the best of these two materials will be the $1.2 \times 10^{19} s/mL$ sample based solely on maximum polarization.

The deuterated samples, however, appear to have longer relaxation times than the two unenhanced samples. This is not surprising because, as was mentioned before, the deuteron tends to lengthen the relaxation time of the other nuclei.

Finally, the carbon-13 relaxation time is the highest of them all but it is difficult to compare because it also occurs at a lower temperature than the others. A good followup experiment would be to obtain more relaxation times at various temperatures so that we can evaluate further the prospects for warming the materials.

Conclusions

Most of the data presented in this paper has been concerned with the hydrogen nucleus. We must always remember that the main purpose of this study is to evaluate materials other than hydrogen that can be used with MRI systems. By the arguments of equal spin temperature (which have held in the carbon-13 urea), however, we can evaluate hydrogen and

extrapolate carbon-13 data. At lower polarizations (which is what we will be concerned with in the warmup process as all polarization will drop off rapidly as temperature rises) we can use the approximation that the carbon-13 polarization will be one-quarter of the hydrogen (one quarter is simply the ratio of hydrogen magnetic moment to carbon-13 magnetic moment). As for the relaxation times, the hydrogen and carbon-13 will be approximately the same in the same host material with the same doping but in general, carbon-13 can be slightly longer. Based on these suppositions, we can be confident that our analysis of the hydrogen nucleus can be transferred, in its essence, to the carbon-13 nucleus.

From the data that we have gathered thus far it is clear that the $1.2 \times 10^{19} s/mL$ urea material is the most promising. The glucose appears to have even more potential than the urea from this data but we need more doping samples to tell for certain.

The next stage in this experiment will be to not only gather more glucose samples but to analyze more relaxations. It is essential to understand the relaxation time response as it changes with temperature. From figure 6 we can see that many minutes are lost over only fractions of a degree celcius. In order for this project to be implemented in vivo, we must warm this material not a few fractions of a degree but rather a few hundred degrees.

It would seem that our polarizations would drop to thermal equilibrium with this kind of temperature increase but that is not the case. The reason that a long relaxation time is required is because, even though it may drop to only a minute or even a few seconds at room temperature, we can still introduce to the patient and image the material in that time if the technique is mastered. This has been done with rats using a different dopant [3]. The preliminary data from that experiment was similar to ours. Their carbon-13 polarizations were slightly higher, 42%, but their relaxation time, 470 minutes, was taken at a temperature of only 1.1K. This time is comparable to our carbon-13 relaxation time but ours was taken at a higher temperature. This is promising for the future of these materials.

References

[1] Most of my understanding of the ideas presented in this paper have been a result of conversations with one of the foremost experts in the field of Dynamic Nuclear Polarization, Donald G. Crabb.

[2] All experiments performed using the UVA Polarized Target Lab equipment.

[3] Ardenkjær-Larsen, et. al. 'Increase in signal-to-noise ratio of $> 10,000$ times in liquid-state NMR.' PNAS. 9/2/2003. Vol 100, no. 18, 10158-10163.