

Magn. Reson. Discuss., referee comment RC1
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Comment on mr-2021-25

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Referee comment on "Solid-state ^1H spin polarimetry by ^{13}C nuclear magnetic resonance" by Stuart J. Elliott et al., Magn. Reson. Discuss.,
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General Comment

In this study, S. J. Elliott et al present a new method to indirectly estimate the proton polarization at dDNP conditions, by exploiting the proton coupling induced asymmetry of the ^{13}C peak of a probe molecule added to the sample (i.e. sodium [2- ^{13}C]acetate). As correctly stated in the motivation of the paper, accurate measurements of proton polarizations at dDNP conditions can be challenging for several reasons (e.g. spurious signal, radiation dumping, lack of appropriate hardware etc.). Using NMR line asymmetric features as a polarimeter is not a new concept in the field. Nevertheless, it has been used in the specific cases of Pake doublet like spectral patterns in the case of 2 dipolar coupled spins (^1H or ^{15}N) or quadrupolar nuclei like ^2H . To the best of my knowledge, this is the first demonstration looking at the asymmetry in a ^{13}C spectrum. This work can be of interest for some players in the field of hyperpolarization. Nevertheless, some crucial points must be addressed prior to any possible publication. I have 3 main general concerns. Spin Hamiltonian of the system; experimental implementation; selling point.

- Where is the asymmetry coming from? Which term of the heteronuclear Hamiltonian causes the splitting? As far as I understood from your phenomenological discussion, you treat this feature as a doublet. Now, besides the fact that I would expect a quartet (see P. F. Barron, *Journal of Organometallic Chemistry*, 236 (1982), 157 – 161), at thermal equilibrium a doublet has no asymmetry. If the coupled nuclear spin ensemble that generates the doublet is not thermally polarized (DNP hyperpolarization for instance), then you observe an asymmetry. A typical example of this technique applied to dDNP is the estimation, after dissolution, of the carbon polarization of [1- ^{13}C]pyruvic acid looking at the asymmetry of the c2 doublet (coupled to the c1, that is enriched). In this study, for zero proton polarization the asymmetry on c2 is huge; for high proton polarization the asymmetry on c2 goes toward zero. So, my question is: what are we looking at? From the NMR spectra, it looks like that when the protons are polarized "another carbon peak" appears on the right or on the left of the main one, depending on "DNP sign".

- Usually, when introducing a new methodology (not yet established and broadly acknowledged), the new methodology has to be compared to the traditional one (i.e. measuring the enhancement from the ratio of the hyperpolarized proton signal to the thermal equilibrium one). In the methods part, you say to have a background free coil. Why don't you use it to show how much your new method is consistent and reliable? Moreover, do you need a methyl group or a simple coupling with a ^1H nucleus can provide the same results? I would have expected at least one more probe molecule, in particular because in the discussion you mention sodium $[1-^{13}\text{C}]$ formate that has no methyl group. Last but not least, when you calculate the asymmetry you take into account the peaks intensity. These peaks are far from being resolved and the intensity of the first will most likely be influenced by the intensity of the second and vice versa. At the end of the discussion you mention the correct data processing procedure to estimate the asymmetry (to deconvolute the two peaks by means of Voigt fits and evaluate the integral). I agree it is less straight forward than just measuring the intensity, but you are introducing a new methodology. You should at least prove that "the peak intensity method" provides, within a decent error margin, the same result of the "the peak fitting method". If you demonstrate that, then we will all use the intensity one, of course.
- In the Methods you put a lot of emphasis on the necessity to have cross polarization to be able to use this method. Firstly, I think that with such a level of deuteration, at 6.7 T and with microwave modulation you should be able to achieve a decent SNR with direct ^{13}C DNP as well (see T. Cheng, PCCP 2013, 15 (48)). Secondly, if CP is required, 90% of the DNP users around the world could not take advantage of this method. Lastly, in the motivation you say that "in lack of ^1H rf coil" your method can be useful...How can you do CP without a proton coil???

IMHO the bare minimum to consider this paper for publication is to address these 3 points: give some theoretical insight about the spectral features; run new experiments to compare the new way of measuring ^1H polarization with the traditional way (preferably using also one more molecule); try without CP.

Specific Comments

Line 11. "is emerging" for a technique invented in 2003 is not appropriate, rephrase like "dDNP allows to prepare proton polarization..."

Line 33. I think there are too many references. You are mentioning hyperpolarization methodology (dDNP, PHIP, SEOP, brute force). I suggest choosing one for each, there is no need to cite 5 or 6 reviews about dDNP. Moreover, the bullet DNP technique from Benno Meier is missing, please include it.

Line 37. Here you can cite more recent papers. A lot has been achieved from 2013 to 2021 concerning human trials. Some suggestions: Kurhanewicz, J. *et al.* Hyperpolarized (13)C MRI: Path to Clinical Translation in Oncology. *Neoplasia* **21**, 1–16 (2019); Chen, H.-Y. *et al.* Hyperpolarized 13C-pyruvate MRI detects real-time metabolic flux in prostate cancer metastases to bone and liver: a clinical feasibility study. *Prostate Cancer Prostatic Dis.* (2019) doi:10.1038/s41391-019-0180-z; Gallagher, F. A. *et al.* Imaging breast cancer using hyperpolarized carbon-13 MRI. *Proc. Natl. Acad. Sci.* **117**, 2092–2098 (2020).

Line 38. It is a super general statement. For sure Prof Jannin is a big player in the field, but I would cite Abragam, Goldman and or Borghini here.

Line 56. This is conclusion not introduction.

Line 65. You use one sample, call it just "the sample", no need to call it **I**.

Line 77. Add brand and model of microwave source.

Line 91. How did you calculate 11 ms? Is there a particular reason (demanding spectrometer duty cycle)? In a solid-state saturation sequence the important thing is that the inter-pulse delay is $> 3T_2^*$. I guess your proton line is 40 – 50 kHz broad. Therefore, the T_2^* is 20 μ s. With an inter-pulse delay of 100 μ s the magnetization in the x-y plane is completely dephased before the next pulse comes and you do not risk flipping back magnetization on z.

Line 95. Is the acquisition time of the FID perturbing the signal? Consider rephrasing

Line 129. The mw gating paragraph is not Methods, it is discussion how it is written here.

Line 151. This paragraph is Discussion not Results. Moreover, the explanation is not clear. Consider rephrasing like: "The microwaves are ON and the ^{13}C nuclear ensemble relaxes towards the spin temperature value it would have achieved in the case of direct DNP (no cross polarization)". Moreover, there is a 3^{rd} factor to consider. The radical concentration and temperature are in the good range for thermal mixing (Guarin et al, JPCL 2017, 8 (22)): the ^{13}C are polarized, the ^1H are saturated. The two nuclear pools most likely exchange energy via the electron non-Zeeman reservoir. This also affects the time evolution of the ^{13}C until ^1H achieves the same spin temperature.

Line 173. Are not mirror images of each other with respect to the x-axis or the y-axis?

Line 196. If you use a stretched exponential, technically, you are not using "a sole" build-up time constant, but a linear combination of many (infinite) build up time constants. Moreover, in the discussion I would like to understand why you observe a stretched buildup. Is beta close to 1 or to 0.5? Please provide the value. Could it be that having

polarized ^{13}C and depolarized ^1H forces a stretched exponential buildup of protons?

Line 214. See general comments for interpretation of the asymmetry.

Line 236. I don't understand this sentence. Can you justify why your calibration curve (pol vs asymmetry) changes slope between positive and negative DNP?.

Line 239. This is discussion.

Line 256. This remains an open question until you don't measure the polarization in the traditional way.

Technical corrections

Line 87. "DNP equilibrium" not "DNP equilibria".

Line 87. I have never heard the term "crusher" rf pulses. Consider using "saturating" rf-pulses.