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# Comment on mr-2021-57

Anonymous Referee #2

Referee comment on "A cryogen-free, semi-automated apparatus for bullet-dynamic nuclear polarization with improved resolution" by Karel Kouřil et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2021-57-RC2, 2021

The manuscript by Kouril et al. describes an improvement of the so-called “Bullet-DNP” technique. In Bullet-DNP a frozen sample is spin-hyperpolarized by dynamic nuclear polarization (DNP) at low temperatures and subsequently transferred in the frozen state to an NMR spectrometer, in which the sample is dissolved and injected into an NMR tube. This process is possible with customized equipment and a special insert for the bore of the NMR spectrometer.

Generally, bullet-DNP provides the possibility to reduce the liquid needed to dissolve the hyperpolarized sample and therefore solution-state DNP experiments can be performed at higher concentrations upon NMR detection.

The manuscript suggests a semi-automatic device to perform these experiments. In comparison to the original setup (suggested by the authors a few years ago) this device is claimed to provide better linewidth as well as easier cleaning procedures of the system’s capillaries and the NMR tube between experiments.

I think that such an improvement is indeed very interesting and worthwhile to be published in Magnetic Resonance. However, I have some doubts about the presentation of the manuscript as well as the performed experiments that the authors should clarify before considering publication of the manuscript.

General comments:

- The manuscript claims a semi-automated device that can lead to a "limit [of] the system to 10 shots per hour". However, the authors only show a single experiment. It would be good to show at least 2 subsequent experiments in order to justify the discussion of throughput and automatization of the system. With conventional systems ca. 5 experiments per day are possible today. In particular, when stating that "[t]he injection device is able to perform multiple experiments without removal from the NMR magnet."
- The linewidth are claimed to be improved with the new setup. However, it is well known to the DDNP community that different line widths can occur between different experiments due to uncontrollable effects (micro or macro bubbles, changing sample volumes, convection etc., scratched in the NMR tube). Is this problem solved with the new device? Again it would be good to show linewidths observed in a few independent experiments
- One claim of the manuscript is the improved cleaning procedure, however, this is described in a single sentence only, if I haven't missed any details: "A cleaning program automatically cleans and dries the device." I would like to read how this automated program works. In addition, how clean are the lines and the tube? Has this been quantified? Do residual contaminations accumulate?

Specific comments.

- The authors claim that conventional DDNP experiments are often not better than normal NMR, stating that 10000 scans are often feasible. How do the authors mean that? At a d1 of 60s (as typical in 13C NMR), this would mean one weak of acquisition. For the pyruvic acid used, a longer d1 would even be necessary.
- The authors state that normally a 100-fold dilution is used for normal DDNP experiments. However, since a few years already many studied have been published using lesser dilution (down to 40-fold and sometimes even less). I would cite such papers, too, (e.g. HyperW experiments from Frydman et al.)
- Relating to the above comment, the propose system is described as "scalable" meaning that the dilution factor can be changed. Again, in my eyes such a claim would be well supported with different experiments at different dilution factors.
- The introduction appears quite incomplete to me. The authors select a few papers to show that DDNP has been applied to metabolomics, DOSY, natural abundance 13C NMR and LLS. However, the selection of references is limited to 7 papers. In addition, it might be useful to cite some of the reviews about applications of DDNP. Even more interestingly, it is stated that multi-dimensional spectra can be detected by DDNP. The cited references describe the used pulse sequences, but the DDNP papers are not cited.
- Relating to the above comment. The authors state that Ardenkjær-Larsen et al., 2018, described their used Cryogenic magnet first (it is true, but the first presentation was actually a conference contribution, the cited paper came later). What about Bodenhausen and co-workers, 2018? This is particular interesting, since the manuscript is going to be published in a Bodenhausen special issue. Besides Kress et al. 2020 has also been missed.
- The used pulse sequence uses $^{1}$H-decoupling. Can the authors compare the effect of the decoupling with a non-decoupled sequence. For singly C13-labeled pyruvic acid, I'm curious what the effect on the main peak will be in the presence of Ox063.
- In Figure 3, the middle line shows the spectrum directly after injection of the bullet, but the signal intensity is very low, compared to the spectrum 3.8 s. How can this be explained?

- The line broadening directly after injection is "attribute[d] to a single large gas bubble that rises inside the NMR tube after injection of the solution". An effect, which is stated as reproducible. Can the authors put the spectral comparisons to the SI? In the main text, they could show a zoom on the main line at during the first 15 scans. To show the change in linewidth.
- Relating to the timing, sometimes the manuscript claims that the second spectrum is recorded at 3.7s, sometimes at 3.8s. Which is correct? Or is this within some experimental error?
- In the downloadable data, I can see some distortions of the spectra until scan 15. Also in figure A1, some "bumps" can be observed in the exponential decay in FID 6 and 10. Could the authors comment on that? How is this relating to the sample stability after 3.7 s?
- Again, concerning the downloadable data: There are 7 signals visible at around 180 ppm. For singly labeled pyruvic acid, I expect less. Or am I mistaken?

Minor comments:

- What is a Bruker NMR spectrometer 2?
- In the discussion it would be nice to read a bit about the applications the authors anticipate for their system. E.g., which other molecules next to pyruvate be explored with bullet-DNP?