A CMOS-based NMR platform with arbitrary phase control and temperature compensation

Reply from the authors

Dear Editor, dear reviewers,

We would like to thank you for consideration of our manuscript for publication in Magnetic Resonance and the overall positive evaluation of our work. The detailed and insightful comments from all reviewers will help us to further improve the manuscript. Please find our point-to-point responses to individual comments below.

With best regards,
Qing Yang
On behalf of all co-authors

RC1

General comments: *The manuscript describes the digital and analog electronics of a portable NMR spectrometer. It consists of a non-commercially available CMOS integrated circuit designed by the authors (TX/RX electronics with RF PA, RF LNA, mixers, IF amplifier, PLL) and of commercially available electronics (DDS chips, multifunction analog/digital board, switches, ...). The operation of the spectrometer is demonstrated with 1H NMR experiments at 62 MHz and 15 MHz using home-made NMR probes consisting of 0.4 and 2 mm diameter solenoidal coils tuned (but not impedance matched) with capacitors. Liquid samples are placed in 0.3 and 1.3 mm outer diameter glass capillary, which tightly fit inside the solenoidal coils.*

The most original contribution of this work is the detailed description of a TX/RX phase synchronization method and of a field drift correction method. Of course, the TX/RX phase synchronization and the field drift are problems which are "solved" in all commercially available NMR spectrometers. However, the merit of this manuscript lies in the fact that the method chosen and the hardware required to solve these problems are described in detail and, hence, can be useful to other groups which are working at the development of compact/portable NMR spectrometers. For this reason, I think that the manuscript deserves to be published

We would like to thank the reviewer for his detailed and overall positive review of our manuscript.

Specific comments:

LINE 23: Typo: "high field homogeneity" instead of "high filed homogeneity"

Thank you for bringing this mistake to our attention. We will correct it in the revised version of the manuscript.

Line 23: "high filed homogeneity" has been corrected to "high field homogeneity".

LINE 35: Typo: "Anders and Boero, 2008" instead of "Anders and Chiaramonte, 2008" (Chiaramonte is not author of that conference paper). Correct also LINE 350.

Thank you for bringing this mistake to our attention. We will correct it in the revised version of the manuscript.

Line 34: The author list has been corrected to "Anders and Boero, 2008", also include the reference in Line 411.

LINE 47: At this point in the manuscript, it is not entirely clear the meaning of "phase-coherent detection of the NMR signal at non-zero IF". A non-zero IF can be produced also with F_LO=F_TX but different from F_LARMOR. In this case there are no phase-coherence issues. Later in the manuscript (LINE 75) it is clear that "non-zero IF" means F_LO different from F_TX, which indeed can produce phase-coherence issues. It is not essential, but maybe I would try to make this clear already at this point of the manuscript.

We agree with the reviewer's opinion and will modify this sentence accordingly. More specifically, we will clarify that the phase-coherence issues we refer to are produced by the fact that F_{LO} is different from F_{TX}.

Line 45: The sentence has been modified to "More specifically, the proposed NMR system provides the possibility of arbitrary phase modulation of the excitation pulse and, even for the case where the receiver local oscillator frequency is different from the excitation frequency, phase-coherent detection of the resulting NMR signal at a non-zero IF by the use of two commercially available direct digital synthesizer (DDS) chips."

LINE 71 (footnote): "Ignoring the inhomogeneity factor". I guess the authors refer to the B1 inhomogeneity which would than produce a non-homogeneous flip angle in the sample (and, in particular, a flip angle which is not 90° everywhere in the sample). It is almost obvious but I would be more clear.

We will revise the manuscript by specifically stating that the inhomogeneity factor is caused by the B_1 inhomogeneity and also the B_0 inhomogeneity.

Line 72 (footnote): The footnote has been modified to "Ignoring the inhomogeneity of the B_0 and B_1 field over the sample volume".

LINE 97: In the given reference (Anders et al., 2010) the impact of gain and phase mismatch on the NMR spectra distortions is not discussed/shown in details. I would suggest to search for references where this issue is discussed/shown more in details.

Thank you for bringing this mistake to your attention:

In the revised manuscript, we will use the following reference instead:

Rahman, A.-u.-., Iqbal., C. M., and Atia-tul, W.: Solving problems with NMR spectroscopy, Elsevier Academic Press, United Kingdom; San Diego, CA2016a.

In section 2.5 of this reference, there is a detailed discussion about how phase cycling can eliminate the imbalance between two channels

Line 113: We have replaced the reference (Anders et al., 2010) by the reference (Rahman et al., 2016).

LINE 107: I would write "NdFeB permanent magnet" instead of "Neodymium permanent magnet". I would also add the value of its typical temperature coefficient (about 0.1%/K at room temperature).

We are happy to use the term "NdFeB permanent magnet" in the revised manuscript. In line 60 of the manuscript, we have mentioned the temperature coefficients of two common magnet materials.

Line 59 and line123: "Neodymium permanent magnet" has been replaced by "NdFeB permanent magnet"

LINE 132: If the scaling factor is selectable from 0.5 to 64, is it correct that the output frequency is between 5.7 MHz and 770 MHz?

This part was unfortunately not well explained in the original version of the manuscript. In fact, a scaling factor of 0.5 refers to the case where an off-chip LO is used instead of the on-chip PLL. This off-chip LO is divided by two to produce the required quadrature signals. In this case, the PA output frequency can in fact go down to DC. However, the usable (TX and RX) output operating frequency range of our platform is limited between 5MHz and 770MHz, where the lower limit is defined by an AC coupling capacitor in the receiver (between the LNA and the mixer.

Line 160-166: A detailed explanation has been added, "Depending on the chip configuration, the on-chip PLL can be used to multiply the external reference frequency by a selectable scaling factor between 1 and 64. Alternatively, the PLL can be bypassed, and the external reference signal is divided by two to produce the required quadrature LO signals from the external reference. In the latter mode of operation, the chip can produce excitation frequencies down to DC, while the minimum detectable frequency in the receiver path is limited by an on-chip coupling capacitor between the LNA and the mixers. Since the on-chip PLL can operate with reference frequencies between 5.7 MHz and 12.1 MHz, overall, the chip has an operating frequency range between 5 MHz and 770 MHz."

LINE 138: I would specifically mention the gain of the LNA and the gain of the mixer (even if it is already mentioned the total RX gain and the gain of the VGA and the gain of the external filter).

Thank you for your comment. We will revise the manuscript accordingly.

Due to the setup of the ASIC it is not possible to measure LNA and mixer gain separately, so we provide the measured conversion gain of the LNA-mixer-combination.

Line173: "The measured maximum combined gain of the LNA and the mixer is 45 dB."

LINE 142: I would mention which specific 130 nm BiCMOS technology has been used for the integrated circuit.

Thank you for your comment. We will revise the manuscript accordingly.

Line 176: "The chip is implemented in a 130 nm SiGe BiCMOS technology offered by STMicroelectronics."

LINE 165: Figure 3b: I would add a scale bar (even if the dimensions are given in the caption).

Thank you for your comment. We will add the requested scale bar.

Line 199: Figure 4b: A scale bar has been added.

LINE 182: Typo (I guess): "...within a few microseconds" instead of "....with a few microseconds"

Thank you for your comment. We will correct this mistake.

Line 220: "….with a few microseconds" has been modified to "…within a few microseconds

LINE 230: Figure 5: I would add a scale bar (even if the coil dimensions are given in the text).

Thank you for your comment. We will add the requested scale bar.

Line 268: Figure 6: A scale bar has been added.

LINE 232: It would be nice to show a picture of the custom made 0.36 T magnet and give some details of it.

Thank you for your comment. We will provide a more detailed description of the magnet.

Line 268: Figure 6: A picture of the custom made 0.36 T magnet has been added.

Line 270-272: A detailed description of the magnet has been added. "The first magnet (B_0=0.36 T), which was used for the relaxometry measurements, is a custom-designed H-shape magnet that features a small volume of $26 \times 9.9 \times 5$ cm^3, a relatively low weight, and a moderate homogeneity of 20 ppm over the sample volume."

LINE 233: I would specify on which volume you have an homogeneity of 20 ppm (I guess it is on the sample volume).

Thank you for your comment. The homogeneity is indeed calculated according to the signal bandwidth over the sample volume. We will state this more clearly in the revised manuscript.

Line 271: The volume has been specified. "…a moderate homogeneity of 20 ppm over the sample volume."

LINE 257: I would specify the repetition time (i.e., the time distance between two consecutive measurements). At first sight, I would have performed many more consecutive measurements than 100. Do you expect any significant difference if 1000, 10000, or more measurements are taken? Which is the origin of the observed standard deviation of the phase? Is it just due to noise present in the signal which set a limit in the standard deviation of the phase or it is larger and due to a residual phase syncronization problem (it is probably possible to run a simple simulation to clarify this point)?

We thank the reviewer for raising this important question. The repetition time used was 1.5 s, which is more than five times of T1, to allow the magnetization to rebuild completely before the next scan. We also performed experiments with a larger number of consecutive measurements with correspondingly larger field/frequency shifts.

In all experiments shown in the manuscript, we synchronized the RX phase to TX phase at the beginning of the pulse, leading to a phase of the NMR signal, which, for a fixed excitation pulse length, varies with the TX frequency (for a fixed pulse length, the phase at the end of the pulse is different for different TX frequencies). We used the rising edge to give the on-chip PLL time to settle to the RX phase defined by DDS2. When using dead times after the pulse that are longer than the PLL settling time, we can also synchronize TX and RX phase at the falling edge of the pulse, removing the problem of phase uncertainty with changes in the TX frequency, allowing for larger number of averages. In the revised version of the manuscript, we will also include these measurements.

Line 297-303: More measurements have been taken. "Additionally, to test the system stability during a long-term averaging measurement, we also recorded 4000 consecutive FID signals over four hours. In these experiments, the proposed field-locking-based temperature compensation scheme was enabled. Table II summarizes the results of this experiment. According to the table, there is a small (below 1 °) increase in the standard deviation of the measured correction phase over time. We attribute this to mainly two effects: First, the adjustment of the excitation frequency sometimes cannot keep up with the temperature drift rate, and, second, the drift of the field homogeneity vs. time. Importantly, the improvement factor due to averaging is close to the theoretically predicted value of $\sqrt{N_{\text{scans}}}$. Figure 7 shows the single scan and time-averaged FID signals using the proposed DDS-based signal generator, an IF of 100 kHz, and a repetition time $T_{\text{R}} = 1.5$ s."

LINE 261: Table 1: It is not clear to me why it is relevant to show also the mean value of the phase. I would specify the number of measurements (10, I guess from the text) and the repetition time. As for the previous case, I would have performed many more consecutive measurements than 10. Do you expect any significant difference if 100, 1000, 10000, or more measurements are taken?

Thank you for your comment. We will remove the mean value from the table. Concerning the expectations for a larger number of measurements, please refer to our answer to your previous question.

LINE 287: Although it might be well known for most of the NMR specialists, I would explain in some more details why "…the predefined pulse length is no longer correct, resulting in distorted CPMG signals".

Thank you for your comment. We will revise the manuscript accordingly.

Line 334: A more detailed explanation of off-resonance effect has been given. "More specifically, if uncompensated, the fixed excitation frequency will gradually deviate from the Larmor frequency over time. In this case, the B_0 field does not completely disappear in the rotating frame, and the effective rotation axis is therefore tilted out of the xy-plane (Korzhnev et al., 2000). In addition, due to less efficient off-resonance excitation with increasing offset frequencies caused by the frequency drift, the predefined duration of the π-pulses might no longer be able to flip the magnetization by 180 °, resulting in distorted CPMG signals."

LINE 295: Figure 9. I would specify the sample used for this measurement. Is it again sunflower oil? T2 is slightly shorter (77 ms) than the one in Figure 8 for sunflower oil (85 ms). As addition to Figure 9a, I would suggest also to add the CPMG "decay" obtained with the temperature induced field drift compensation scheme.

Thank you for your comment. The sample is the same sunflower oil. However, the experiments were conducted with almost one month in between, and the sample was not protected from light. We will therefore rerun both experiments with fresh sunflower oil and show these data in the revised version of the manuscript. In Fig. 9a, the correct attenuation line is obtained based on the temperature compensation scheme. We will modify the manuscript accordingly.

Line 328-329: The experiments have been rerun. "The corresponding relaxation times derived from single exponential fitting were $T_2 = 89$ ms and $T_1 = 95.4$ ms, respectively."

Line 344: "More specifically, the mean and standard deviation of all recorded T_2 values in Fig. 10b are 88.5 ms and 0.4 ms, respectively,"

LINE 296: It is not clear to me if and why the measurements with heterogeneous samples are relevant to qualify the phase-synchronization and field-correction approach proposed in this paper. Of course, these are additional nice measurements that can be included in the article but their "relevance" for the main messages of the paper is not fully clear to me.

Thank you for your comment. We merely used the measurements on the heterogeneous samples as an example for 2D relaxation measurements since the duration of such experiments is typically much longer and a field-correct approach is almost mandatory.

LINE 308: Table II: I wonder if it make sense (and it is correct in metrology terms) to specify the T2 and T1 values with so many significant digits (I guess not but I'm not sure).

Thank you for your comment. We will revise the manuscript by stating only statistically relevant information (no digits after the decimal dot).

Line 361: Table III has been modified.

LINE 310: Figure 10: I would mention the Cu concentration in the figure caption or directly in the figure (even if these number are given in the text).

Thank you for this suggestion. We will add the Cu concentration in the figure caption.

Line 362: "…two different concentrations of copper sulfate doped water (5 mM and 75 mM)."

LINE 325: I would add a few citations to the articles corresponding to "….our EPR-on-a-chip transceivers".

Thank you for your suggestion. We will add more references to the revised manuscript.

Line 386: "…our recent EPR-on-a-chip transceivers (Chu et al., 2018; Hassan et al., 2021) for enhanced sensitivity in order to open up new application scenarios for portable NMR systems."

"Aesthetic" comment: for my personal taste, there is an excessive use of footnotes. I would move all current footnotes (or the large majority of them) in the main text

Thank you for this “aesthetic” suggestion. We are happy to modify the manuscript accordingly.

RC2

General comments: *The manuscript represents an important increment in the capabilities of integrated CMOS-based NMR systems. As the authors say, such systems, in combination with compact permanent magnets, have the potential to extend the usefulness of NMR spectroscopy, imaging, and relaxometry into domains where portability is a paramount concern. The paper gives a very useful and compact account of the relevant literature. It improves on the previous state of art in two key respects. On the one hand, an elegant solution is provided to allow phase-coherent signal acquisition at non-zero IF (with an IF significantly larger than the spectral window). This enhances sensitivity as it allows the receiver to operate above the influence of 1/f noise. On the other hand, a temperature/frequency compensation is built in that allows to compensate for magnetic field drifts, and corresponding shifts in Larmor frequency, due to temperature fluctuations.*

The manuscript is well written, and the argument is supported by clear and carefully designed figures. It is a nice addition to the existing literature, and should be published in Magnetic Resonance.

We thank the reviewer for his overall positive review of our manuscript.

Specific comments:

L75ff. In the discussion of the phase control approach, the manuscript uses the term "off-resonance", if I interpret this correctly, to mean a frequency that is different from the excitation frequency, not from the Larmor frequency. I find this confusing, since "off-resonance", in the NMR context, typically refers to a situation where the excitation pulse frequency is different from the Larmor frequency. This then requires higher pulse power, etc. The paragraph should be reformulated to make this clear. It may be best to avoid the term "off-resonance" altogether, because of its inherent ambiguity (off resonance to what?).

We thank the reviewer for this important comment. In our notation, the term "off-resonance" refers to the fact that the excitation frequency is identical the receiver local oscillator (LO) frequency but different from the Larmor frequency. In this case, there is no phase coherence problem since the excitation and the LO frequency are identical. The term "on-resonance" refers to a situation where the excitation frequency is identical to the Larmor frequency but different from the receiver LO frequency. In this case, phase coherence of consecutive measurements is not guaranteed and measures, such as the ones proposed in the manuscript, have to be taken to obtain phase coherence of signals from consecutive scans.

- L94. Typo: low-filed should be low-field

Thank you for bringing this mistake to our attention. We will correct it in the revised manuscript.

Line 109: “low-filed” has been corrected to “low-field”.

- L200, Figure 4. Would a plot of oscillator phase vs time (as opposed to amplitude vs time) make the argument more easily accessible to the reader?

Thank you for this excellent suggestion. We will include such a plot of phase vs time in the revised manuscript.

Line 237: Figure 5b and 5c: A phase response has been added in Fig. 5.

- *L286: "[...], changes of the ..." This sentence is correct but awkward - reformulate?*

Thank you for your comment. We will rewrite the sentence in the revised manuscript.

Line 334-335: The sentence has been modified to "More specifically, if uncompensated, the fixed excitation frequency will gradually deviate from the Larmor frequency over time.".

- *L288: What is the mechanism that leads to the described artefacts in the CPMG data due to magnet drift? (This may be well known, in which case a reference would be helpful)*

The artifacts in CPMG arise from the time-varying deviation of the excitation frequency from the Larmor frequency, resulting in time-varying off-resonance effects. Here, the proposed calibration scheme removes these artifacts. We will explain this effect in more detail in the revised manuscript.

Line 334-338: A more detailed explanation of off-resonance effect has been given. "More specifically, if uncompensated, the fixed excitation frequency will gradually deviate from the Larmor frequency over time. In this case, the B_0 field does not completely disappear in the rotating frame, and the effective rotation axis is therefore tilted out of the xy-plane (Korzhnev et al., 2000). In addition, due to less efficient off-resonance excitation with increasing offset frequencies caused by the frequency drift, the predefined duration of the π-pulses might no longer be able to flip the magnetization by 180 °, resulting in distorted CPMG signals."

- *L290ff: In addition to rectifying temperature drift effects in CPMG measurements, would the approach also be capable of doing the same for spectral resolution, in a situation where signal averaging over an extended period of time is required? What would be the limitations? If this could be done reliably, it could significantly reduce the complexity of permanent-magnet NMR spectroscopy systems.*

The first condition for the proposed scheme to work is that there is sufficient signal quality to extract at least one spectral component, i.e. the Larmor frequency of one type of spins inside the sample, from a single shot experiment. Next, a change of field inhomogeneity with temperature, which cannot be compensated in a straightforward fashion with the proposed method, will cause artifacts in the averaged spectrum. Under such conditions, more elaborate compensations would be required. We will revise the manuscript to mention this limitation of the proposed scheme.

Line 376-382: "Here, we would like to point out that, despite its overall good performance and usefulness for stabilizing the average B_0 field, the presented field-locking-based temperature compensation scheme cannot compensate for changes in the field homogeneity over time, which can lead to reduced frequency resolution in the averaged signal. Moreover, the proposed approach relies on sufficient SNR in a single shot experiment to extract the current Larmor frequency with sufficient precision. Finally, the update rate for the estimation of the Larmor frequency is limited by the experiment's repetition rate, potentially leading to limitations in the presence of relatively fast temperature fluctuations."

- *L308ff, Table II: the SI unit for concentration is either "mmol/l" or "mM". "mM/L" does not make sense.*

Thanks for pointing out this sloppy mistake. We will correct it in the revised version of the manuscript.

Line 361, All concentration units in this paper have been modified to mM.

RC3

General comments: *This manuscript describes an interesting novel CMOS-based NMR platform. Fully integrated NMR-on-a-chip approaches are around for a long time already, starting of with the seminal work of Giovanni Boero and his coworkers at EPFL. The novelty of the current design is that it allows arbitrary phase control without compromising the timing of the pulses. Furthermore, the authors use the dual DDS system to implement a frequency-field lock to adapt the frequency of the excitation pulse to the field of a drifting magnet of e.g. a permanent magnet without thermal stabilization. It is an overall interesting manuscript that deserves publication.*

The paper is well-written but very technical, I think the first part is somewhat beyond the imagination of much of the readership of "magnetic resonance" and would be more fitting in a more engineering focused journal. The experimental validation is convincing, however, and very accessible for the magnetic resonance community.

We thank the reviewer for his overall positive review of our manuscript and we will modify our paper to make it more accessible to the readership of "Magnetic Resonance".

Specific comments: *I have some remarks relating to the "temperature compensation". What the system does is adjust the frequency of the excitation pulse to the variation of the magnetic field strength, so I would not call this temperature compensation. This is called a frequency-field lock and has been used already in the early days of NMR to acquire spectra in unstable magnets. Notably it has also been used to signal average NMR signals in ultra-high-field Bitter magnets which display temporal instabilities because of inlet cooling water temperature variations and ripple of the power supply. In those cases, the signal of a separate reference signal was used to track the field variations. In the current implementation the frequency is adjusted based on the frequency variations in the signal of the sample of interest. This precludes signal averaging for samples with very low signal intensity, as the SNR of a single scan needs to be high enough to allow the determination of the frequency shift due the magnet field drift. Furthermore, I think that signal averaging in a permanent magnet without any temperature regulation will not only suffer from drift of the magnetic field, but also there will be temporal variations of the homogeneity due to temperature gradients, so even with the frequency-field lock the resolution will deteriorate. If a separate reference signal would be acquired simultaneously this could be addressed by reference deconvolution. I feel these considerations should be discussed in the paper.*

We fully agree with all of the reviewer's statements. We will therefore revise the manuscript by properly mentioning the great similarity of the propose approach with classical field locking. The reason why we proposed the "field-locking-based temperature compensation method", which makes use of the NMR signal itself and zero padding instead of a dedicated lock channel to minimize complexity, is that it can be very easily added in the digital domain if the proposed 2-DDS-based frequency synthesizer is used, rendering it very convenient for CMOS-based NMR platforms utilizing permanent magnets.
We also fully agree that a simply tracking of the Larmor frequency is not enough to compensate for temperature induced changes of the magnetic field distribution over the region of interest. We will modify section 2.2 to discuss these points in greater detail in the revised version of the manuscript.

Line 127-144: A detailed discussion about field stabilization has been added. “Actively adjusting the static B_0 field by means of a field-frequency lock (FFL) is another common method to stabilize the field over time. This approach uses a feedback control based on real-time measurements of an NMR reference signal, frequently of a nucleus other than the under observation in the main channel, in an auxiliary NMR channel that is operated in parallel with the main channel (Hoult et al., 1978; Kan et al., 1978; Chen et al., 2018). With this method, the magnetic field can be stabilized at sub-ppm levels of accuracy over several hours of measurement time (Takahashi et al., 2012). Alternatively, a high-precision Hall sensor can also be used to monitor the B_0 field over time (Lei et al., 2017). One drawback of the conventional FFL method is that it requires a dedicated lock channel, significantly increasing the hardware complexity, especially for low-cost portable NMR systems. As an alternative to adjusting the B_0 field, the feedback loop in the FFL method can also be closed by modifying the excitation frequency to follow the measured changes in the Larmor frequency (Issadore et al., 2011; Lei et al., 2015). Here, it should be noted that all FFL-based methods that use a single field probe to measure the B_0 field can only be used to control the average B_0 field, but cannot compensate for temperature induced changes of the field homogeneity, which can largely deteriorate the achievable frequency resolution when averaging over a long time. Therefore, several signal processing techniques based on the measured NMR signal can be used to complement the abovementioned hardware measures to improve system robustness against temperature fluctuations further (Morris et al., 1997; Ha et al., 2014). Among them, a compensation method based on reference deconvolution is widely used to obtain a high-resolution NMR spectrum in the presence of spatially fluctuating B_0 fields (Morris, 1988; Barjat et al., 1995; Iijima and Takegoshi, 2008). In this approach, the ideal spectrum is reconstructed by deconvoluting the measured (main) NMR spectrum with the ratio of the measured and the ideal reference signals.”