

# SINGLE CHIP PROBE FOR HIGH RESOLUTION MAGIC ANGLE COIL SPINNING NMR OF BIOLOGICAL SAMPLES

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## ABSTRACT

We report a single-chip probe for “magic angle coil spinning”-MACS nuclear magnetic resonance (NMR) spectroscopy. The probe consists in a wirebonded microcoil integrated with an on-chip interdigitated capacitor. This LC-circuit is resonant at 500 MHz (<sup>1</sup>H Larmor frequency at 11.7 T) enabling wireless inductive coupling of the NMR signal and spinning for high resolution NMR. We demonstrate stable spinning up to 110 Hz of the probe containing 330 nl water sample. The probe successfully withstands the large centrifugal forces as well as the eddy current heating. We prove increased spectral resolution down to 5.6 Hz (11 ppb at 500 MHz) as an effect of spinning at 110 Hz.

**KEYWORDS:** metabolomics, Magic Angle Coil Spinning, microcoil, nuclear magnetic resonance

## INTRODUCTION

In this paper we address two well-known issues in NMR spectroscopy for microscopic samples: sensitivity and resolution. Magnetic resonance based methods inherently offer a low sensitivity and this has been one of the limiting factors in what concerns their integration in LOC devices. There are several main research directions to overcome the sensitivity problem of the NMR experiment: increasing the strength of the magnetic field ( $B_0$ ) of the NMR spectrometer since the sensitivity is increasing with the  $7/4^{\text{th}}$  power of  $B_0$  [1], polarization transfer from optically pumped nuclei in order to compensate for the small population difference between the upper and the lower energy states [2], and the design of the RF pick-up coils essentially by downscaling them to closely conform to the size- and volume-limited target samples [3, 4]. We have recently addressed this issue [5] by reporting a robust, MEMS-compatible process to fabricate 3D solenoidal microcoils for applications in microscale magnetic resonance imaging (MRI). The process relies on the unique capabilities of an automatic wire bonder in conjunction with traditional MEMS techniques. We have also performed an in-depth characterization of the wirebonded microcoils for MRI purposes [6].

The importance of NMR spectra resolution is crucial for instance in metabolomic applications to differentiate among close metabolites signals. Usually spectral lines are significantly broadened in any condensed phase by nuclear spin interactions up to the point where they become featureless and hard to interpret, especially when very small chemical shifts are involved. A well-known method to improve NMR spectral resolution is the magic angle spinning (MAS): the sample is spun at very high rotational speeds (up to 70 kHz) about an axis which is tilted at a very precise angle – the “magic angle”,  $\theta_m=54.74^\circ$  – with respect to the static magnetic field  $B_0$  as shown in Figure 1. By spinning, the time-dependent nuclear spin interactions – chemical shift anisotropy and quadrupolar interactions – are averaged to non-zero values, while the spinning together with tilting at the magic angle averages to zero the dipole-dipole interaction thus yielding higher resolution NMR spectra.

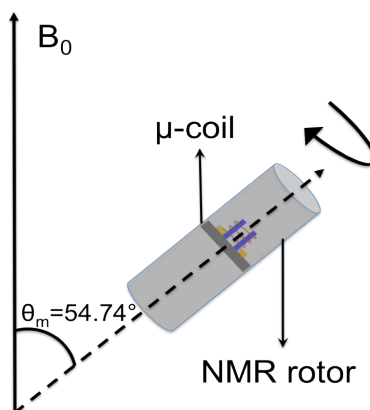


Figure 1. Schematic of the NMR experiment: the probe is placed inside a commercial NMR rotor and spun at rates up to 70 kHz about an axis tilted at the “magic angle” ( $54.74^\circ$ ) with respect to the main magnetic field. Spinning the sample at the magic angle averages out time dependent interactions experienced by the nuclear spins thus leading to narrower linewidth and finer spectra.

## THE MAGIC ANGLE COIL SPINNING TECHNIQUE

In the classical MAS configuration, the sample holder alone is spinning while a static coil is used to pick up the NMR signal being directly connected to the NMR spectrometer via wires tethered at the coil terminals. However, the main issue associated with this approach is the limited filling factor of the coil used for signal pick up, and this problem is especially severe for microscopic samples. The recently reported [7] magic angle coil spinning (MACS) methodology addresses this issue by wrapping the detector coil around the sample holder and spinning both the coil and the sample simultaneously. The pick up coil is tuned to the Larmor frequency of interest and the NMR signal is wirelessly inductively coupled to the static coil of the spectrometer used for spin manipulation. This approach also maximizes the filling factor of the detection coil. Using the MACS technique the signal sensitivity for microscopic sample has been increased by one order of magnitude compared to standard NMR [7].

Here we combine for the first time the MACS technique with an on-chip NMR probe for microscopic samples created using MEMS processing and wirebonding technology for the detector microcoil. The solenoidal wirebonded microcoil is integrated on-chip with an interdigitated capacitor thus forming an LC resonant circuit which is designed to resonate at the Larmor frequency of interest. In this paper the measurements have been performed in a static magnetic field of 11.7 T which corresponds to 500 MHz Larmor frequency for the proton ( $^1\text{H}$ ). However, the probe fabrication technology (wirebonded microcoil [8] and on-chip capacitor) provides full flexibility in choosing the number of capacitor fingers as well as, in the last fabrication step, the number of coil windings to precisely tune the probe at the frequency of interest – in this case 500 MHz. The NMR signal is coupled inductively, i.e., no wires are tethered to the terminals of the microcoil therefore enabling sample spinning.

## FABRICATION

The fabrication process of the NMR probe described in Figure 2a is very similar to the process previously presented in ref. [5]. Basically, a Pyrex substrate is used in order to avoid eddy current formation and sputtered with a CrAu (50/500 nm) layer, which is subsequently patterned by UV photolithography to obtain the contact pads for the microcoil wirebonding step and the interdigitated capacitors integrated with the microcoils. After electroplating to a thickness which accounts for the skin depth of Au at the operating frequency the seed layer is removed by wet etching. Therefore, no additional technological step needs to be performed compared to the structure reported in [5] apart from the inclusion of the interdigitated capacitors which is done in the design phase. Since the space in an NMR rotor is very limited, the footprint of the chip has to be minimized. To this end, the interdigitated capacitor was completely embedded in SU-8 in order to increase the capacitance by the dielectric constant of SU-8 ( $\epsilon_r=4$ ). Finally, the hollow cylinders 650  $\mu\text{m}$  high and 1 mm in diameter were manufactured by thick SU-8 photolithography to serve as sample holders and mechanical support for coil winding, which is the last step in the process flow. A picture of a fabricated device is shown in Figure 2b having an interdigitated capacitor with 3 overlapping fingers and a wirebonded microcoil with 13 windings.

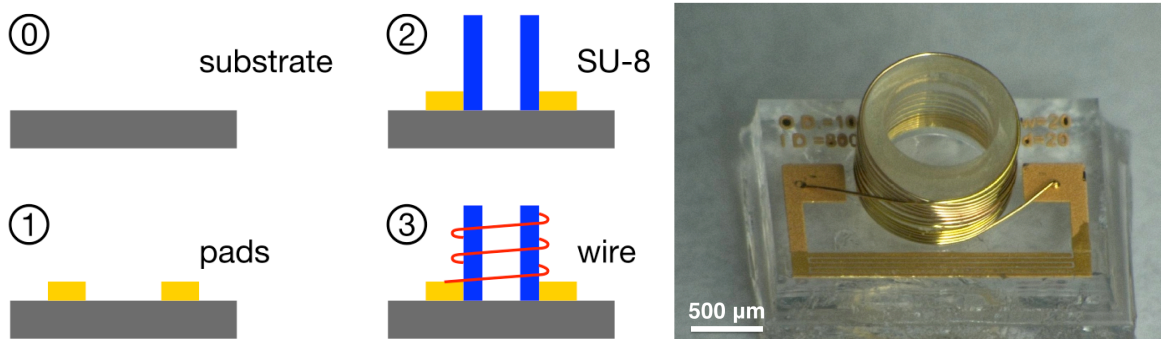


Figure 2. a) Schematic of the fabrication process flow for the NMR probe; b) Microscope image of a MEMS fabricated NMR probe resonant at 500MHz. The capacitor has 3 overlapping fingers (0.53 pF) and the wirebonded solenoidal microcoil has 13 windings (190 nH).

## RESULTS AND DISCUSSION

In order to get meaningful information about the biochemical activity of a biopsy, high-resolution NMR analysis could be the approach of choice owing to the valuable molecular level insight. As explained above, MAS NMR essentially averages the susceptibility variations which can be present in such a biological tissue this narrowing the line-widths with higher rotational speeds. However, fast spinning can be a problem for bio-samples and living organisms because the large centrifugal forces acting on the sample can damage the tissue. Moreover, the heat generated during the fast rotation in a very strong magnetic field can also damage the biological sample. For this reason high speed MAS is rarely the preferred method for the study of biological tissues where the preservation of morphological structure is required.

On the other hand, slow spinning MAS could be an option for the NMR analysis of biological samples. The main problem

associated with slow spinning is the existence of the spinning sidebands which complicate the spectrum analysis. The spinning sidebands are clearly visible in Figure 3a for a water sample spun at a relatively low speed – 110 Hz. The spectral separation of the sidebands is equal to the spinning frequency, therefore it is clear that for higher spinning frequencies the sidebands spacing would be larger, rendering a more complicated spectrum with different yet close metabolite signals easier to interpret. We have chosen the 110 Hz spinning frequency because at this value the sample heating due to eddy currents is limited (less than  $2^\circ$  [9]) thus enabling in-vivo experiments. With respect to our previous spectroscopy measurements [10] using a similar detection coil, we demonstrate here a significant decrease in the water spectral linewidth due to spinning. Figure 3b shows that the width of the central water peak is 5.6 Hz which equalates to 11 ppb at the frequency of interest, as compared to 15.2 Hz in Ref. [10]. This result has been obtained without any susceptibility matching around the microcoil.

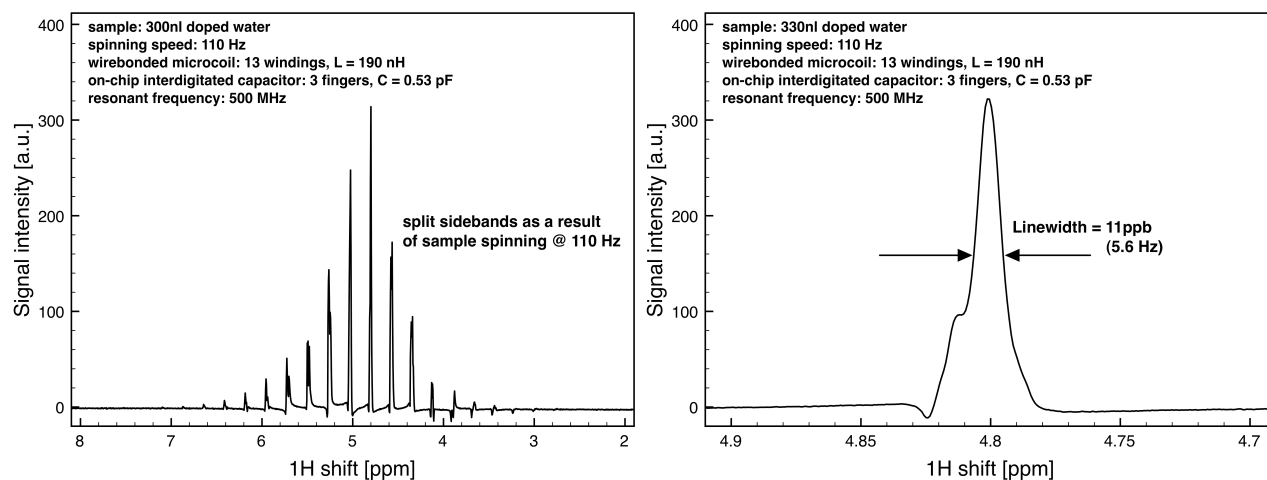


Figure 3. a)  $^1\text{H}$  NMR spectrum of 330 nl water spun at 110 Hz. Due to spinning the central water peak is split in sidebands spaced at 110 Hz, i.e. 0.27 ppm at 500 MHz; b) Central water peak narrowed down to 5.6 Hz, i.e. 11 ppb at 500 MHz.

The spinning bands in Figure 3a as well as the non-perfect Gaussian shape of the water peak in Figure 3b are due to the susceptibility mismatch among the different constituent materials of the probe, mainly because of the Au in the pads, capacitor and coil wire. Further improvement is underway by replacing Au with Cu and redesigning the probe with radial symmetry about the spinning axis, e.g., the tuning capacitor can be designed with radial symmetry around the coil.

## CONCLUSION

In this paper we report the combination between our fabrication technology for 3D solenoidal microcoils as MR sensors and a relatively new NMR methodology – the magic angle coil spinning technique. The single chip NMR probe is not affected by the heat dissipated due to the eddy currents arising as an effect of spinning in an intense magnetic field and is mechanically robust to withstand the centrifugal forces at 110 Hz. This spinning speed is relatively low compared to usual MAS speeds and the increased spectral resolution demonstrated here shows the potential of our NMR probe for in-vivo high resolution NMR for metabolomic applications.

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