3D SOLENOIDAL MICROCOIL ARRAYS WITH CMOS INTEGRATED AMPLIFIERS FOR PARALLEL MR IMAGING AND SPECTROSCOPY

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ABSTRACT

We present high-performance MR imaging and spectroscopy results obtained with wirebonded solenoidal microcoils manufactured in a MEMS-integrated technology. We report MR testing of 400µm inner diameter solenoidal microcoils for imaging of Eremosphaera Viridis algal cells with 10µm isotropic resolution. NMR spectroscopy has been performed on a water sample obtaining a linewidth of 0.04ppm. The newly introduced MEMS technology naturally lends itself to the fabrication of microcoil arrays, thus enabling parallel high-throughput MR investigation. As a proof of concept we report flip-chip integration of a microcoil-array with a CMOS amplifier array. "Teflon grease" has been used as phantom and three spectra have been acquired simultaneously yielding a linewidth of 0.5 kHz and a spin sensitivity in the frequency domain of 10^{15} spins/$Hz^{1/2}$.

INTRODUCTION

State of the art

The sensitivity of the MR signal is dramatically enhanced when the pick-up coils closely conform to small samples and this concept has been introduced in early 90's by Peck et al. [1] and McFarland et al. [2]. As a consequence, a lot of effort has focused to find a robust, wafer scale process for microcoil fabrication. Maybe the most straightforward attempt to fabricate submillimeter coils is essentially the hand-winding technique reported by Peck et al. [1]. Although the reported diameters are down to 50 µm, the manual processing is an obvious drawback. Microcontact printing followed by electroplating of a microcoil around a capillary tube represents another solution employed for instance by Whitesides et al. [3]. Here the disadvantage is that after the actual processing step, each coil has to be individually manipulated and contacted. A MEMS-compatible process has been reported by Dohi et al. [4] combining surface micromachining and a post- release folding process followed by electroplating. To summarize, most of the previously reported attempts to manufacture solenoidal microcoils for NMR/MRI applications are either delicate techniques or serial processes incompatible with batch-fabrication, thus directly affecting reproducibility and yield.

The IMTEK team has recently reported a robust technology for reliable wafer-scale fabrication of solenoidal 3D microcoils [5, 6]. This technology exploits the characteristics of an automatic wirebonder in conjunction with traditional MEMS processing.

The feasibility of using the wirebonded microcoils for MRI applications has been proven in a recent communication [7] while in [8] a more detailed investigation of the capabilities of such a MR probe is given. In this paper we present for the first time MR imaging using actual cellular samples as well as the first NMR spectroscopy results using the wirebonded microcoils.

Concerning the integration with electronics, the EPFL team has already reported a very compact, full CMOS-technology device [9] which integrates planar micro-coils with detection electronics. However, integration of 3D solenoidal microcoils is lagging behind mainly because no valid process for wafer scale fabrication has been reported so far. The problem is solved here where we report for the first time hybrid integration of an array of 3D microcoils with CMOS electronics and the first NMR spectroscopy results taken with such an array.

SINGLE MICROCOIL

Single microcoil – fabrication details

The fabrication process of the microcoils has been presented in detail in refs. [5, 7]. Briefly, a Pyrex wafer is sputtered with a layer of CrAu (50/500 nm), which is patterned using UV photolithography and wet etching to define the contact pads for the coils. Non-conducting substrates are used in order to prevent eddy current formation. Next step consists in defining the cylinders that act both as mechanical support for the subsequent coil-winding step and as sample holder. To this end, a thick layer (650 µm) of SU-8 2150 is cast on the wafer and UV-patterned.

Employing SU-8 photolitography to define the supporting pillar of the microcoil, enables a high flexibility in defining the microcoil dimensions. The height of the microcoil can be adjusted through the thickness of the SU-8 layer while the lateral dimensions (diameter and sidewall thickness) are defined by photolithography. In our previous reports [7, 8] we have tested the MR capabilities of a 1 mm outer diameter solenoidal coil while here we report for the first time MRI/NMR results of a microcoil with 500 µm outer diameter and 50 µm sidewall thickness. The flexibility in tuning the sidewall thickness allows placing the windings closer to the sample thus increasing the filling factor of the microcoil.

Single microcoil – imaging and spectroscopy

Eremosphaera Viridis algal cells have been chosen for imaging due to their robustness and relatively large dimensions (150 µm diameter). Two such cells have been loaded into the SU-8 sample holder and this has been subsequently covered with an adhesive film (ABgene, Fisher Sci GmbH) to prevent the evaporation during image acquisition. Figure 1 shows the microcoil after the MRI scan with the wire removed in order to visualize the cells loaded in the SU-8 sample holder.

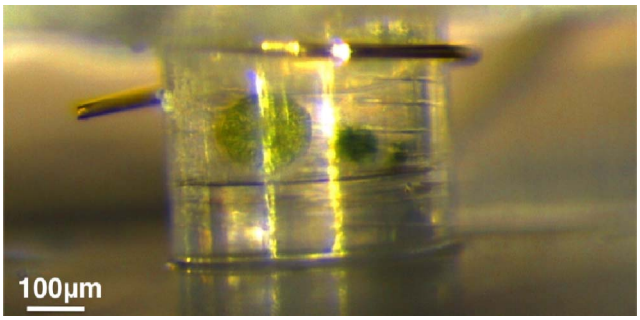

Figure 1: SU-8 sample holder loaded with two Eremosphaera Viridis cells after removing the 25µm diameter insulated Au wire. Process details: refs. [3-5].

MR single-cell images were acquired on a 9.4 T Bruker Biospec animal system using a 3D gradient echo (GE) sequence with: TR/TE=600/12 ms, resolution 10×10×10 µm^3, leading to a scan time of 12 h. The microcoil, the sample holder and the sample introduced into the MR scanner, slightly disturb the highly uniform B_0 field. This happens because the materials have different magnetic susceptibilities and in order to correct for the global and local field variations a second order iterative global shim procedure has been applied using the shim coils available in the MR scanner. Figure 2 displays a coronal view (parallel to the surface of the coil) of the sample where the two cells are clearly visible.

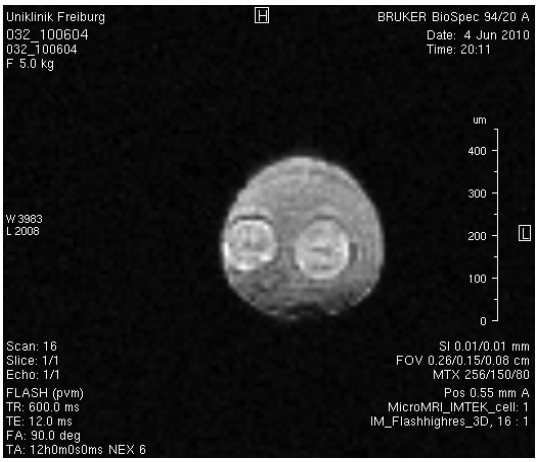

Figure 2: Coronal slice from an MR with 10µm isotropic resolution and SNR=36.7. The two cells are distinct and clearly visible. (Scan performed on a Bruker 9.4T small bore animal scanner).

Spatially localized proton spectra of water were acquired using a single voxel PRESS (Point-RESolved Spectroscopy) sequence (TR/TE=2500/20 ms, 64 averages). After performing localized shimming on the selected PRESS voxel of 127×80×80 µm^3 (~ 0.8 nL), the water spectrum was acquired after 2 min 50 s scanning time (Figure 3). A spectral linewidth of 0.038 ppm (15.2 Hz) and SNR=30 were obtained. The linewidth is rather large compared to previously experimentally achieved values as reported for instance in [10]. This result is mainly due to: (*i*) high susceptibility mismatch between the Au wire (χ_{Au}=-34×10^{-6}) and the surrounding materials (~ -10×10^{-6} for sample and SU-8 container); (*ii*) the shimming is rather inefficient for such small volumes. Further improvements involve replacing the Au wire with Cu as well as building dedicated micro-shimming systems.

This data nevertheless nicely demonstrates the ability of wirebonded solenoidal microcoils to resolve single-cell structure through high resolution MR microscopy and to perform localized spectroscopy of nanoliter voxel size in a short scanning time.

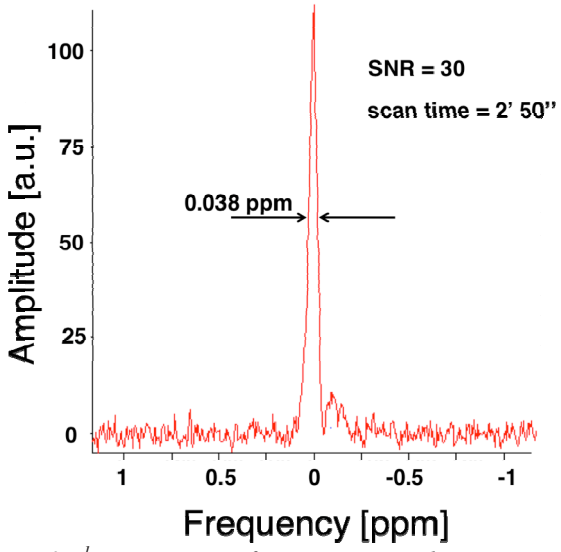

Figure 3: ^{1}H spectrum of water acquired using a mono-voxel spectroscopy technique (PRESS, TR/TE = 2500/20 ms, voxel size = 127x80x80µm^3). An SNR=30 was obtained for only 2min 50s scan time. (Scan performed on a Bruker 9.4T small bore animal scanner).

WIREBONDED MICROCOIL ARRAY

For imaging, an array of receivers can increase the field of view while maintaining the spatial resolution. Moreover, such an array can be used for parallel spectroscopy, drastically increasing the throughput of NMR spectrometers.

Employing MEMS techniques to fabricate the solenoidal microcoils enables us to manufacture wafer scale planar arrays and this represents an essential step towards high-throughput MRI/NMR investigation. In this paper we report hybrid integration of an array of four wirebonded microcoils (Figure 4) with CMOS amplifiers.

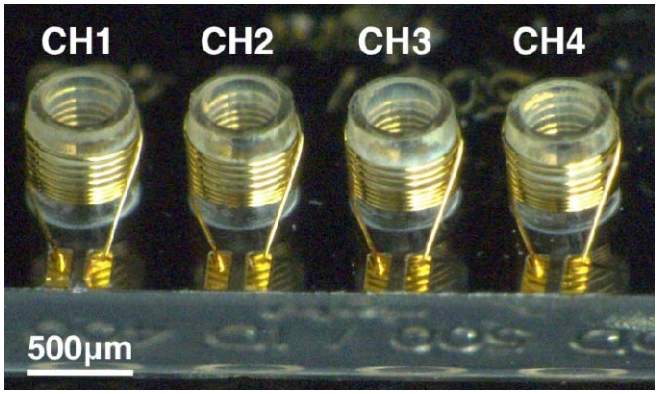

Figure 4: Array of wirebonded microcoils.

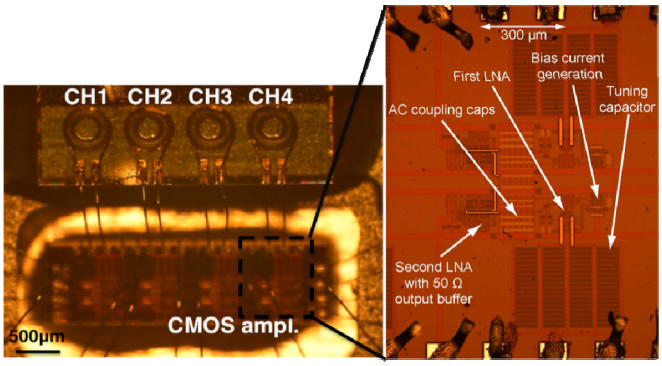

Figure 5: Microphotograph of the 4-channel microcoil-preamplifier assembly. Inset: Zoom-in of the integrated electronics.

Preamplifier module

A custom integrated low-noise preamplifier module has been designed in 0.35 µm CMOS technology. The preamplifier module connected to the microcoil array is shown in Figure 5. The on-chip electronics consists in two low-noise amplifier (LNA) blocks and a 50 Ω buffer. The electronics in a single channel has an input referred voltage noise density of 1.7 nV/√Hz at both 300 MHz. The on-chip gain at 300 MHz is 42 dB. Together with the preamplification from the tuned LC-detection circuit the integrated gain is large enough to produce robust signals with noise levels that render the noise contribution of all other electronics in the reception chain negligible. The on-chip tuning capacitor is realized as a MOSFET-based differential varactor which can be tuned to capacitance values between C_{min} = 3.5 pF and C_{max} = 8.7 pF, allowing a coil with an inductance of 40 nH to be tuned at 300 MHz to perform NMR experiments in a magnetic field of 7 T.

One major advantage of the custom preamplifier-coil assembly is the potential of avoiding losses associated with interconnections. Furthermore, due to the close proximity to the detection coil and the high input impedance of the preamplifier, matching capacitors are not needed, drastically reducing the space requirements for a single detection channel. Therefore, owing to the co-integration of the varactor-type tuning capacitor, relatively dense arrays of NMR receivers become feasible as demonstrated by the assembly shown in Figure 5.

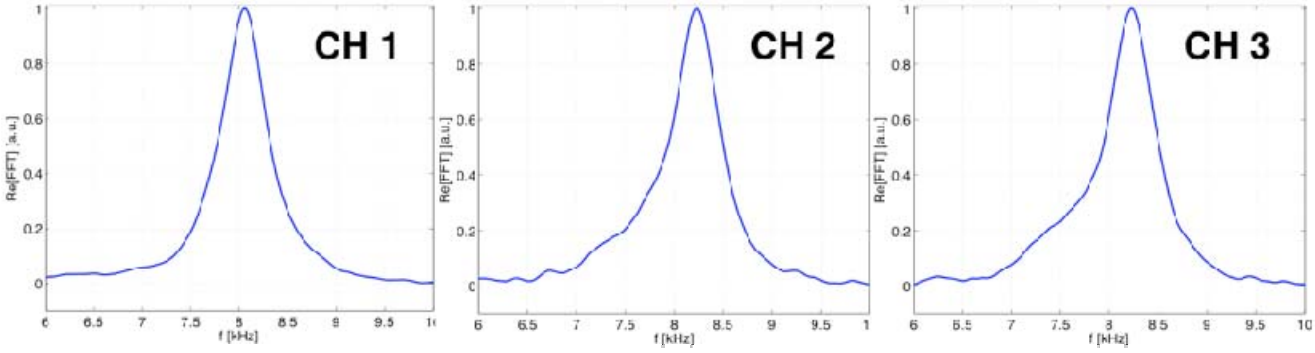

Figure 6: Real parts of the FFTs simultaneously acquired from 3 out of 4 channels of the array using Teflon grease as a sample. (Measurements performed at 7T in a vertical bore NMR spectrometer)

Parallel spectroscopy

In order to demonstrate the possibility of performing parallel spectroscopy, NMR spectra have been taken in a 7 T magnet at EPFL using a grease with a high hydrogen content (Finish Line, New Technology) as a sample. Following a 90°-pulse the free induction decay (FID) was recorded for each channel and the real part of the corresponding fast Fourier transform (FFT) is displayed in Figure 6 for 3 out of 4 channels available. A time-domain matched filter corresponding to the T_2* time of the sample of about 750 µs was applied. The calculated spin sensitivity in the frequency domain is 10^{15} spins/Hz$^{1/2}$ and was calculated as explained in detail in [9]. These spectra demonstrate not only the potential of high-throughput parallel spectroscopy but also the measurement reproducibility using the hybrid assembly microcoil – CMOS electronics.

CONCLUSION

Combined wirebonding and SU-8 technology offers the possibility for further microfluidic integration with potential applications in high-throughput, parallel NMR-based diagnostics and metabolomic monitoring.

We also report hybrid integrated reception array involving 3D wirebonded solenoidal microcoils and CMOS

amplifiers. This further demonstrates the potential for the co-integration of a large number of reception 3D micro-coils with CMOS chip in a densely packed array.

ACKNOWLEDGEMENTS

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