HIGH SIGNAL TO NOISE RATIO IN LOW FIELD NMR ON CHIP, SIMULATIONS AND EXPERIMENTAL RESULTS.

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ABSTRACT

A μ fluidic chip with integrated microcoil was developed for Nuclear Magnetic Resonance (NMR) spectroscopy on limited volume samples (nanoliters range). This chip will be used for the online monitoring of micro chemical reactions. Design rules for the microcoil to achieve the best Signal to Noise Ratio (SNR) were obtained by finite element simulation. For pure water in a low field NMR magnet (60 MHz i.e. 1.4 Tesla) a SNR of 550 was achieved which is to our knowledge higher than any other μ fluidic chip with integrated detection coil. It is also shown that a spectral resolution of 0.025 ppm is obtained when a microchannel with an arbitrary cross section is placed parallel to the magnetic field. A high SNR at low magnetic field for small volume samples is essential for the development of portable NMR systems where mini permanent magnets of 1 Tesla are used.

1. INTRODUCTION

There is an increasing effort to perform chemical reactions in μ fluidic chips. Some of the goals are to decrease the amount of expensive chemicals that are used for the reactions and a better thermal control of the reaction. A consequence is that only a small amount of product is available for analysis. This has led to the downscaling of analytical techniques such as mass, infrared and Raman spectrometry, UV, fluorescence and electro chemical detection and also Nuclear Magnetic Resonance (NMR).

NMR is a powerful technique which can identify chemical compounds by the unique composition of electromagnetic proton resonance frequencies in a large magnetic field. Relative to many other analytical techniques, however, it is inherently insensitive [1]. Since the signal scales with the square of the static magnetic field (B_0), one of the main aims in NMR has been to increase B_0 , which has currently led to 21.1 Tesla NMR magnets. Magnets with a large field (> 2 Tesla) are typically superconductive, quite large and expensive which limits the use of NMR to large chemical laboratories.

NMR on limited volume samples (nanoliters range) can be achieved by placing a μ fluidic chip with integrated detection coil inside a conventional NMR magnet [2, 3]. A future goal for NMR on chip is the use of small magnets to obtain a mini NMR system, which can be integrated into more complex μ fluidic systems. The small sample size is an advantage in this case since the homogeneous part of the magnetic field can be small which is easier to obtain. NdFeB magnets have a field strength of about 1 Tesla which is large for permanent magnets but relatively low for NMR spectroscopy. Together with the small sample volume, this makes a high performance detection coil one of the key factors for the development of such a mini NMR system.

This paper reports on the design and fabrication of a μ fluidic chip which was used to measure NMR spectra of limited volume samples (56 nl) in a conventional low field 60 MHz NMR magnet (1.4 Tesla, Varian EM360L).

2. NMR SIGNAL AND COIL DESIGN

The amount of signal that can be retrieved from a sample depends on the total volume and the static magnetic field strength in the following way [4]:

$$S \propto B_0^2 \cdot r_s^3, \quad (1)$$

with S the signal level, B_0 the magnetic field strength and r_s the sample radius. This shows that scaling down the sample has a dramatic effect on the signal intensity. To maintain a reasonable signal the coil must be scaled down to be close to the sample. In our case a planar microcoil is used, which can be defined by the number, height, width and separation of the windings and the inner coil radius (Figure 1).

Figure 1: Schematic cross-section of the micro coil with three windings on top of a μ fluidic chip.

The magnetic field that is produced by a microcoil (B_1) carrying a unit current can be calculated (Figure 2). The B_1 field inside the sample area is proportional to the NMR signal intensity [4]. The main noise source in the system is the electrical resistance of the coil (Johnson Noise) [5]. Increasing the number of coil windings results in a higher NMR signal. On the other hand, every additional winding also increases the electrical resistance and noise of the coil. Stocker et al. [6] analytically calculated the optimal number of turns for a maximum Signal to Noise Ratio (SNR) while taking these two effects into account. The electrical coil resistance at high frequencies increases more than linearly due to the skin effect and eddy currents. The effect of the eddy currents on the resistance is difficult to calculate analytically. An estimate for the upper limit of the resistance was calculated by Eroglu et al. [7], but only for specific conditions.

In this paper the SNR of the microcoils is simulated using the finite element method. Finite Element Method Magnetics (FEMM) is a freely available tool for analysing 2D and axisymmetric electromagnetic problems [8]. The round spiral planar coil is approximated by 3D circular turns that can be

simulated in an axisymmetry problem. A simulation of a coil with 18 windings on top of a V-shaped channel is shown in Figure 2.

Figure 2: Typical cross section of the B_1 field lines simulation by FEMM [8].

For every simulation the width of the windings (w) and inner coil radius (r_i) were fixed and the maximum SNR was calculated by varying the number (N) and height (h) of the windings. The separation between the windings (s) was kept equal to w . The SNR of the simulations was calculated by dividing the total B_1 field in the sample by the square root of the total resistance. A small contact resistance (R_c) of 0.1 Ohm was included to obtain realistic noise levels. Figure 3 shows the maximum attainable SNR for several winding widths as calculated by FEMM. Simulations in this figure are for a copper coil in air at 300 MHz, with the centre of the sample located 250 μm below the coil. Note that the number and height of the windings are listed in Table 1 for every point.

Figure 3: SNR_{max} versus winding width (simulation). Each SNR_{max} value has its own coil parameters (see Table 1). Frequency is 300 MHz and r_i is 250 μm in these cases.

The simulation shows the general trend that windings with a smaller w and s result in a better SNR. Those coils have high aspect ratio windings, which makes them difficult to fabricate. Hence the general design rule for planar NMR coils is to take the minimum w and s possible, and use FEMM to calculate the optimum number and height of the windings.

Table 1: The simulated SNR_{sim} (values plotted in Figure 3).

w [μm]	h [μm]	N	SNR_{sim} Incl. R_c [a.u.]
2	17	138	6.41
6	15	42	5.62
10	14	24	5.00
15	15	15	4.71
25	26	8	4.56
40	38	5	4.45
70	60	3	4.11
100	78	2	3.53

Resolution improvement

NMR magnets produce a very homogeneous B_0 field which is necessary for a good resolution. Any object with slightly different magnetic permeability that is placed in this field, (e.g. a $\mu\text{fluidic}$ chip) can disturb this homogeneity. Careful design, choice of materials and placement of the chip in the B_0 field are therefore necessary to maintain a good resolution (the typical minimum resolution to perform NMR spectroscopy is about 0.1 ppm). E.g. the irregular shape of the microcoil can disturb the homogeneous B_0 field. Trumbull et al. [9] used a combination of chromium and gold to match the magnetic permeability of the coil to air. Stocker et al. [2] placed the coil in a special fluid (Fluorinert) of which the magnetic permeability was matched with the coil material. Although placing the coil very close to the sample will give much NMR signal, at some point this will negatively influence the resolution [1, 2]. The shape of the sample volume also influences the field homogeneity. Massin et al. [10] predicted and measured a higher resolution for ellipsoid like sample volumes. In this paper a different approach is followed. It is clear that the magnetic field lines are disturbed when there is a sudden change in magnetic permeability, e.g. going from glass to the sample. Any change of channel geometry near the detection coil will (nearly always) negatively influence the field homogeneity. This will not be the case if a long sample channel with a constant shape is used. The abrupt beginning and ending of the channel will disturb the homogenous magnetic field. But in the middle of the channel where the coil is placed these entrance effects have little influence and the field is more homogeneous.

3. EXPERIMENTAL SET-UP AND MEASUREMENTS

Two Borofloat glass wafers were powder blasted [11] to obtain the channels and through holes of the chip (see Figure 4). The powder blasting process gives a rough surface and the cross section of the channel has a rounded V-shape. The wafers were direct bonded and annealed at 600°C. The wafer stack was thinned down on one side by HF etching to decrease the distance between the coil and the channel to about 80 μm (see Figure 1). A copper coil was electroplated on top of the channel.

Figure 4: The glass NMR chip with planar micro coil. Chip size is 1x1 cm, channel size is 500 μm .

Three types of coils were designed; the dimensions and simulated properties are listed in Table 2. The height for each coil was 15 μm and r_i is 250 μm . The optimum height for maximum SNR is actually larger and will be employed in the next chip series. The V-shaped channel is 500 μm wide at the top, and 450 μm deep. This leads to a sample volume below the inner coil radius of about 56 nl (note that the volume underneath the windings also contribute slightly to the NMR signal).

Table 2: Simulated values at 60 MHz for three types of coils.

Type	w&s [μm]	N	L [nH]	R [Ω]	SNR _{sim} [a.u.]
I	20 & 20	18	360	4.73	1.00
II	30 & 30	12	158	2.32	0.95
III	80 & 70	4	15.7	0.31	0.87

NMR set-up

The electronic set-up for NMR was copied from Massin et al. [3]. The NMR chip was placed on a holder, filled manually with pure water and matched and tuned to 50 Ohm at 60 MHz by using two variable capacitors. The holder was then carefully positioned in the conventional 60 MHz NMR magnet (Varian EM360L) with the μ fluidic channel in line with the large magnetic field. A single 90° pulse with a length of 28 μsec initiated the NMR measurement. The NMR time signal was acquired by an Agilent oscilloscope (54621A) and Fourier transformed to the frequency domain by Agilent VEE software. All acquisition parameters (e.g. acquisition time, number of data points, filter settings etc.) were kept constant. The resolution (in parts per million: ppm) was defined as the Full Width at Half Maximum (FWHM) of the peak in the frequency domain divided by the NMR frequency of 60 MHz. The SNR in the frequency domain was calculated by dividing the peak height by the rms noise value between 540 and 600 Hz (9 and 10 ppm).

Results

A single NMR measurement is shown in Figure 5. In total 15 chips have been measured with at least 8 measurements per chip. The resolution ranged between 0.019 and 0.074 ppm from chip to chip. We believe local differences in the power

blasted channels are responsible for these differences in resolution.

Figure 5: NMR spectrum of pure water. Type I coil, single scan, SNR = 550, FWHM = 1.3 Hz, resolution = 0.022 ppm.

The SNR that is measured in the frequency domain depends on the exact coil to channel distance (ranging from 60-110 μm), and on the resolution (not the peak height but the area of the peak is related to the total NMR signal that is retrieved from the sample). To properly compare several SNR measurements with different resolutions the SNR value is multiplied with the square root of the FWHM [10]. Secondly, SNR measurements from one coil type with different channel to coil distances were combined to calculate the SNR* $\sqrt{\text{FWHM}}$ for that type at a channel to coil distance of 80 μm . These final values are shown in Table 3.

Table 3: Average values of the SNR times the square root of the resolution in comparison with the simulated SNR.

Type	SNR* $\sqrt{\text{FWHM}}$ [$\sqrt{\text{Hz}}$]	norm.	SNR _{sim} [a.u.]	SNR _{sim incl. R_c} [a.u.]
I	648	1.00	1.00	1.00
II	584	0.90	0.95	0.89
III	280	0.43	0.87	0.49

The average values of SNR* $\sqrt{\text{FWHM}}$ are also normalised with respect to the type I coil value. The SNR* $\sqrt{\text{FWHM}}$ values can be compared with the simulated SNR values which shows that the agreement is not good. Especially for the type III coil, where a value of 0.87 relative to the type I coil was expected from simulations, and a value of 0.43 was measured. This is on account of the high R_c of 0.8 Ohm, due to long (7 cm) and thin (70 μm) copper wires that were used to connect the chip. After including this R_c in the noise level, the simulated SNR values are much more in line with the measurements (last column in Table 3).

Resolution

Placing the chip in the NMR magnet with the channel perpendicular to the large field (in the wrong way), resulted in a resolution of no more than 0.5 ppm. With the same chip a resolution of 0.022 ppm was obtained when placed correctly in the magnet, which shows the importance of a proper chip orientation. The good resolution is reflected in the NMR spectrum of ethanol, which reveals the spin coupling of the triplet (Figure 6).

Figure 6: Single scan NMR spectrum of 100% Ethanol measured with a type I coil (see Table 2).

4. DISCUSSIONS

The measured relative performance of each coil type was correctly predicted by simulations. The type I coil with the smallest w and s produces the best SNR, as expected. The typical SNR of 550 is better compared to other authors, as shown in Table 4. This is remarkable since our magnetic field is five times lower, which gives an inherently 25 times weaker signal.

Table 4: Comparison of NMR results with other authors (coil and channel integrated in chip). Results obtained with water.

Freq. [MHz]	Volume [nl]	SNR	Resolution [ppm]	ref.
250	393	41	0.012	[9]
300	30	260	0.100	[10]
60	56	550	0.022	This paper

Several reasons are responsible for this. Firstly this coil design was fully optimised while taking into account the eddy currents. Secondly, the effect of eddy currents and skin effect on the coil resistance is not so large due to our low working frequency. In addition, the contact resistance does not degrade the SNR much in our case due to the relatively high coil resistance. Finally, the low NMR frequency (60 MHz) makes it possible to use coils with a high self-induction (L). This high L results in a low coil resonance frequency which prevents the coil to be tuned to high NMR frequencies for use in large magnetic fields. In that case the optimum SNR is limited by the maximum L that allows resonance at the frequency of interest. Further improvement of the SNR in our system can be achieved by getting the coil closer to the channel and by decreasing the width and separation of the windings. Simulations also indicate that a coil with an inner radius that is smaller than the sample radius also improves the SNR.

5. CONCLUSIONS

This paper reported on the design and fabrication of a μ fluidic NMR chip. The finite element simulations of the micro detection coils qualitatively agreed with the measurements. The general design rule for planar NMR coils

is to take the width and separation of the windings as small as possible and calculate by simulation the number and height of the windings that result in the largest Signal to Noise Ratio (SNR).

In a five times lower magnetic field (theoretically giving a 25 times lower signal) a SNR was measured which is even higher compared to results from other authors. The good spectral resolution of 0.022 ppm was achieved by simply placing the long μ fluidic channel in parallel with the magnetic field. Any entrance effects that disturbed the homogeneity of the field are in this way brought far away from the detection coil, and have little influence at the sample volume. Spin coupling of the ethanol triplet was observed. Further project aims are the monitoring of chemical reactions online on chip, and the development of a portable mini NMR system using small magnets. The high SNR at a low magnetic field and small sample volume achieved in this paper makes such a system possible.

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