Silicon-Cylinder nano liter NMR-probe for biomedical analysis systems

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Introduction

Metabolic profiling, i.e. the qualitative and quantitative analysis of small metabolite molecules in biomedical fluids, provides an insight into the biochemistry of living things. NMR-spectroscopy is in principal an ideal technique for metabolic profiling, and is already widely used for abundant samples, since it permits the identification and quantification of metabolites within one simple one pulse NMR-experiment. Limited samples like adult haematopoietic stem cells from human umbilical cord blood - our target samples - will only be accessible for NMR-spectroscopic analysis, if amount/volume matched NMR-probes are available.

We present a new NMR-micro-probe designed for the analysis of sample volumes in the range of 10 nl to 50 nl. It is based on spiral micro-coils in a Helmholtz configuration which is housed in a silicon cylinder for susceptibility matching purpose (Fig. 1 and 2). The sample is applied to the probe via an exchangeable quartz capillary. Results, with respect to sensitivity (B_1/i), and spectral resolution are given for a single layer spiral coil (Fig. 2) as well as for a Helmholtz configuration and put into context with already published micro-probes [1].

Methods

The micro technological fabrication of the susceptibility matched, proton and carbon free, silicon cylinder Helmholtz micro-coil is going to be described elsewhere. Planar spiral micro-coils with five copper windings of 20 µm x 20 µm width and height and an inner diameter of 380 µm were built (Fig 1). Water was used as sample to test the NMR-spectroscopic performance of the NMR-probe in the Helmholtz and in a single coil configuration shown in Fig. 2. The proton resonance frequency was at 750 MHz (wide bore Bruker Avance spectrometer). The samples were placed in quartz capillaries (20 mm length, o.d. 330 µm, i.d. 200 µm, Vitrocom Inc.) and sealed with low melting wax. Water plugs with varying length (0.4 mm = 13 nl, 0.6 mm = 19 nl, 1.2 mm = 38 nl and full length of the capillary) were placed in the capillaries using a home built fluid manipulation system based on 5 µl to 100 µl Hamilton syringes.

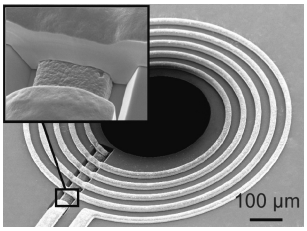

Figure 1: SEM micrograph of a coil layer, magnified view of conductor cross point

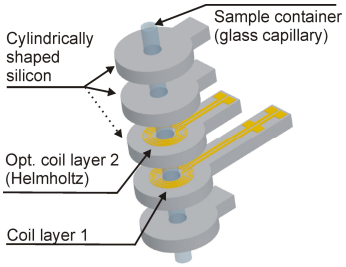

Figure 2: Silicon-cylinder micro coil

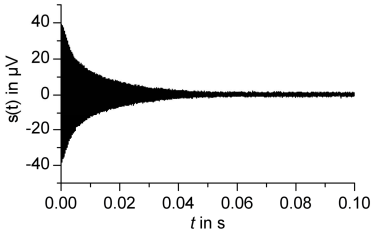

Figure 3: Time domain signal of a single scan: 90° pulse length = 4µs, pulse power = 52 mW, Δt= 8 µs, t_{acq} = 0.26s, filter bandwidth = 125 kHz, number of scans = 1; Signal amplitude at t_0=39.2 µV, noise amplitude = 410 nV.

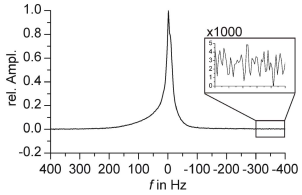

Figure 4: Spectrum of a single scan: line width ~21 Hz, SNR_f = 840, $S_m(H_2O)$ = 405 µmol^{-1}

Results

For the silicon cylinder single layer spiral coil (Fig. 2), to which we will restrict ourselves for this abstract, we obtained a 4 µs / 90° pulse with 52 mW RF-power. The signal to noise ratio (SNR) for a single scan of 38 nl water in the time domain was determined to be SNR_t=95.6 (Fig. 3). The line width in the frequency domain was measured to be 21 Hz and the accompanying SNR_f=840 (Fig. 4). That corresponds to a molar water sensitivity of $S_m(H_2O)$ = 405 µmol^{-1} . Hence the mass limit of detection (LID), i.e. the amount needed to obtain a SNR_f=3 was determined to be $LID_m(H_2O)$=7.4 nmol. The application of matched weighting as outlined in ref. [2] yields SNR_f=2397. In that case the LID decreases by a factor of 840/2397=0.35 to $LID_m(H_2O)$=2.6 nmol.

Discussion

We present a new, very sensitive, susceptibility matched micro-coil based NMR-probe for mass limited samples. The sample is easily exchangeable by replacing the capillary. No extra micro-fluidic channel system is needed, as in most of the micro coil systems [1,3]. In our setup the solute volume is reduced to a minimum, since the entire sample is placed within the active region of the NMR-micro coil. This minimises the needed amount of the mass limited sample. Scaling the results for SNR_f and linewidth given in ref. [1] from 300 MHz to our spectrometer frequency of 750 MHz, shows that our coil has a better spectral resolution 21 Hz (0.028 ppm) instead of 0.1ppm [1], which can be attributed to our susceptibility matching silicon cylinder. Neglecting possible sources of additional losses at higher frequencies, the weighted SNR_f in [1] can be extrapolated to be 3076 and therefore indicates a slightly higher sensitivity (factor 1.3) of the concept in ref. [1].

References

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