Supporting information for:
Continuous flow $^1$H and $^{13}$C NMR spectroscopy in microfluidic stripline NMR chips.

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Technical details NMR stripline chips

In general, the chips are composed of substrates of glass or fused silica (outer dimensions 25 mm x 10 mm). The stripline structure is copper electroplated (15 µm thick) onto the substrate using a 200 nm/15 nm thick copper/chromium seed/adhesion layer. The ground planes are applied on both sides of the stripline structure as electroplated Cu on substrates or as copper foil. At each side of the stripline, fluidic microchannels were etched or diced.

Figure S1: NMR stripline chips used in this study: chip (A), chip (B), chip (C), d) shows the schematic cross section of chip (A) and (C). e) shows the schematic cross section of chip (B).

Design A: The stripline chip has two microfluidic channels into which the inlet and outlet capillaries are fastened by ceramic glue. The chip is made of 4 substrates of 100 µm thickness (D263T borosilicate, Schott) on which the copper stripline structure and shieldings are deposited, and microfluidic microchannels are isotropically etched. After mounting in the probe, the two halves of the probe hold the stripline together and make the ground connection. Fused silica capillaries (Polymicro Technologies, 75 µm ID, 150 µm OD) are glued into the inlet and outlet (Ormocer ceramic glue). The stadium-shaped detection volume is approximately 400 µm wide and 150 µm deep. Microchannel detection volume of
a single microchannel: 140 nl (3 mm strip) (note that the stripline design makes use of two microchannels, on either side of the chip, possible). The thickness of the chips is 460 µm.

b) Design B: The stripline chip has one microchannel diced into the substrate into which a FS capillary containing the sample can be placed. The chip is made out of two fused silica substrates (500 µm thick). On one side the copper stripline structure is deposited. The two parts are bonded using FEP foil (fluorinated ethylene propylene; type 100C20, thickness 25 µm, DuPont) at 250 °C and a pressure of ca 70 bar. Both parts contain a diced groove of 400 x 400 µm, through which a FS capillary (250 µm ID, 360 µm OD) is loaded which is used as the microfluidic microchannel. Copper foil is used as shielding on both sides without bonding, short circuit is separately soldered onto the chip. Single microchannel sample volume: 150 nl, Thickness of the chip: 1100 µm, excl. shielding foils.

c) Design C: Similar design as chip (A), but made in thicker glass substrates (150 µm). Therefore, the fluidic microchannel is also wider and the connecting FS capillaries have a larger diameter (100 µm ID, 200 µm OD). Single microchannel detection volume: 245 nl (channel width: 400 µm, channel depth: 200 µm, 3mm length strip) Thickness of the chip is 630 µm.

**Fabrication details of fused silica stripline NMR chips**

The base material of the NMR-chips is fused silica. Figure S2 shows an overview of the fabrication process of high-sensitivity stripline chips. Prior to sputter-deposition of a metallic copper-chromium thin-film on the frontside of fused silica substrates (100 mm diameter, thickness 525 µm, double-side polished; universitywafer.com), the substrates are cleaned using immersion in fuming 100% nitric acid for 10 min (Selectipur 100453, BASF) and boiling 69% nitric acid (VLSI 116445, BASF) for 15 min, followed by quick dump rinsing in demineralized water and spin-drying. Sputter-deposition at room temperature (argon pressure 0.67 Pa; Ar purity 99.999%) is done on a home-built DC-magnetron sputtering system. A
Figure S2: Overview fabrication steps for high-sensitivity stripline NMR-chips in fused silica (DSP: double side polished; IBE: ion beam etching)
Figure S3: Schematic representation (a), topview image (b) and cross-sectional images (c-e) of high-sensitivity stripline-based NMR-chips in fused silica. In b) the cross-sectional view-line x-x is indicated of which c)-e) are images. In f) a schematic cross-section indicates where images c)-e) are taken.
15 nm layer of chromium (target purity 99.95%; Kurt J. Lesker) is used as adhesion material for the 200 nm thick copper seed layer (target purity 99.999%; Kurt H. Lesker). Deposition from 2 inch targets is done without breaking the vacuum. Onto this metallic film a 24 µm thick layer of high-aspect ratio photoresist (AZ9260, AZ Electronic Materials; MicroChemicals GmbH) is spin-coated, which is patterned by means of standard UV-lithography. The pattern defined in the photoresist resembles the stripline structure, onto which a 15 µm thick copper layer is electroplated. Amongst other parts, the home-built electroplate set-up comprises a glass container with the electrolyte solution and a power supply (Dynatronix, model DuPR10-1-3) to accomplish plating of copper on the seed layer. The applied DC current density is 0.75 A per square decimeter of seed layer surface area. In order to obtain a uniform copper layer, during electroplating at room temperature, the electrolyte solution near the surface to be plated is continuously refreshed by means of vertical movement of a sprayhead (fully immersed in the electrolyte) at 30 mm distance of the surface and recirculation of the electrolyte with a pump (Masterflex). A volume of 10 liter electrolyte contains 1 kg copper salt (copper(II)-sulfate-pentahydrate, Schlötter Galvanotechnik GmbH), 1.1 liter 96% sulphuric acid (VLSI UN1830, BASF), 1.5 ml 50% hydrochloric acid (VLSI UN1790, BASF), 100 ml HL11 starter and 2.5 ml HL13 grain refiner (Schlötter Galvanotechnik GmbH), and de-mineralized water added to reach the given volume. After reaching the targeted Cu thickness (after ∼ 36 min), the substrate is thoroughly rinsed with de-mineralized water to prevent oxidation of the electroplated metal. Subsequently, the photoresist is removed with acetone (VLSI 100038, BASF), followed by removal of the Cu/Cr-seed layer by means of ion beam etching (Oxford i300 with in-situ SIMS end point detection system; Argon pressure 0.3 mTorr, temperature 25 °C, current ∼ 122 mA). In the backside of this substrate a 400 /µm wide and deep groove/slit is diced, which is aligned with respect to the electroplate copper structure (Disco DAD-321 dicing machine; thermo-carbon TC-400 dicing blade, 25 krpm rotational speed, 6 mm/s feed speed), followed by dicing into samples of 25 mm × 10 mm. In a blank fused silica substrate a groove/slit chamber with similar dimensions is
diced, followed by division into samples of 20 mm × 10 mm. The difference in length of the samples is required to be able to electronically contact the copper structure after assembly of the NMR-chip.

A stack of a sample with copper and a blank sample is realized in a home-built mold, which is used to ensure that both sample chambers are well-aligned with respect to the stripline as well as to each other. In-between the two samples, a sheet of fluorinated ethylene propylene (FEP) is placed (FEP type 100C20, thickness 25 µm, DuPont). After clamping of this stack configuration in a home-built clamping tool, this tool is loaded into a vacuum furnace (modified Heraeus system, with Edwards pressure controller). The temperature of this system is increased to 260 °C, at which it was maintained for 4h. This temperature in combination with the load on the stack (ca. 70 kg/cm²) ensures that the FEP bonds onto the copper/glass of the samples above/below the sheet, and that the FEP sheet is squeezed between the copper structures, which is a requirement to minimize distortions in the magnetic field (i.e. susceptibility match). Last step in the fabrication process of these stripline NMR-chips is finalization of the stripline geometry by means of assembly of separate copper foils on both sides of the FEP-bonded glass-stack. Prior to mounting of configured stripline chips in the probe of the NMR measurement set-up, fused silica capillaries (PolyMicro Technologies; outer diameter 360 /mum, inner diameter 250 /mum) are inserted in the grooves/slits, which serve as fluidic chambers. Figure S3 shows a series of images of high-sensitivity stripline-based NMR chips. In Figure S3a a fully assembled chip is shown. In Figure S3b a schematic topview is given with outer dimensions. Figures S3c-e are cross-sectional images along the line x-x’ shown in Figure S3b: both diced grooves/slits are well-aligned with respect to each other and the stripline (Figure S3c), and this FEP-sheet indeed fills the gaps in the Cu-structure near the stripline (Figures S3d and S3e). The small gap underneath the FEP foil visible in Figure S3d is an artifact caused by the cross-sectional cutting procedure.

Of the above-mentioned process, the steps substrate cleaning, sputtering of Cu/Cr, lithography on AZ9260 photoresist and stack-alignment should be done in a cleanroom environ-
ment, to avoid problems with dust-particles. In our case clamping at elevated temperatures and dicing was also done in a cleanroom, but this is not a necessity. All other process steps, i.e. electroplating and finalization of the chips with copper sheets, are done in non-conditioned laboratory environments.

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Homebuilt probeheads

Two homebuilt probes were used in this work; a single resonance probe with a $^1$H channel and a double resonance probe with a $^1$H channel and a variable frequency X-channel. In the probe design symmetry and simplicity of the probehead are of great importance. The single resonance ($^1$H) probe consists of a long aluminium cylinder, divided in two halves. The chip and circuit board exactly fit into trenches at the top of the probehead. The stripline structure is connected to tuning capacitors on one side and to ground on the other side by soldering. The return line connection is given by direct contact between the copper planes and the aluminium cylinder. This parallel rf circuit is capacitively coupled and matched to the 50Ω rf-connection. The tuning- and match capacitors (small Voltronics non-magnetic quartz trimmers and DLI non-magnetic ceramic chip capacitors) are mounted on a printed circuit board (PCB) and placed in one of the two halves of the aluminium cylinder. The rf circuit of the single resonance ($^1$H) probe is shown in Figure S4a.

In the double resonance (HX) probe, the stripline chip is placed in a gold-plated copper cylinder, divided in two halves, both with milled trenches fitting the chip. The stripline is inserted as a short circuit at one side and soldered to a two channel tuning- and matching
circuit on the other side. Both channels have capacitors connected to ground for tuning and series capacitors for matching end coupling with the NMR transmit/receiver channels. The X-channel is equipped with a parallel LC-filter circuit to block the $^1$H frequency entering the X-channel. The tune- and match capacitors are mounted on a platform just below the chipholder and connected with a handformable coaxial cable to the rf-connectors. The chipholder is mounted in the center of this platform. The tune/match platform is mounted on top of an aluminium tube which is part of the probe housing. The rf circuit and pictures of the double resonance (HX) probe are shown in Figures S4b to S4d.

Figure S4: Schematics of the rf circuits of single resonance $^1$H probe (a) and double resonance HX probe (b), pictures of the double resonance HX probe showing (c) the stripline chip on top and the electronic and microfluidic connections on the bottom, and (d) the opened top of the probe with the microfluidic FS capillaries connected.

Microfluidics

For pumping the solution through the stripline NMR chip, one or two syringe pumps (NE-1000, New Era Pump Systems Inc.) were used, with syringes (1 to 5 ml, luer lock gas tight, SGE Analytical Science and VWR), connected by approx. 3 m long fused silica capillaries
(360 μm O.D., 250 μm I.D., Polymicro Technologies) to the top of the probe. For chip (A) and (C) (S1), a union (Upchurch Scientific, P-779) was used to make the connections to smaller diameter fused silica capillaries (chip (A): 150 μm O.D., 75 μm I.D., chip (C): 200 μm O.D.,100 μm I.D., Polymicro Technologies), which were glued into the inlet and outlet of the chip. At the outlet another union (Upchurch Scientific, P-779) was used to connect to a wider capillary (360 μm O.D., 250 μm I.D.) that led to a waste glass container at the bottom of the magnet. The connections to larger diameter FS capillaries at the inlet and waste lines were used to prevent buildup of pressure in the system. For chip (B) a fused silica capillary (360 μm O.D., 250 μm I.D.) runs through the chip, which was only fixed at the top to prevent motion, by leading it through a hole in a TEFLON disc. The FS capillary is connected to syringe pump and waste in the same way as with chips (A) and (C).
One-dimensional $^1$H spectra

Figure S5: $^1$H NMR measurement in continuous flow, acquired in the single channel $^1$H probe equipped with chip (A). A) Ethyl crotonate (20 vol% in CDCl$_3$), at a constant flow rate of 1 $\mu$l/min, single scan. B) Menthol (30% in CDCl$_3$), with a constant flow rate of 15 $\mu$l/min, single scan. Zero filling up to 32000 points and 3 Hz line broadening was applied for both spectra.