

Titel des Vorhabens: Micro scale resonators for nuclear and electron spin resonance spectroscopies “MicroRes”

Projektnummer/Aktenzeichen: T62/2019

Executive Summary

In this project, we developed self-assembled rolled-up microcoils for NMR. These coils belong to the smallest coils ever used for NMR, and they are competitive with other commercially available as well as hand-made NMR coils regarding sensitivity and resolution. In addition, we can produce them in high yield and easily integrate them into a microfluidic system. We did not achieve a combination of NMR and ESR detectors. Instead, we further improved our NMR microcoils regarding resolution and sensitivity, integration into a microfluidic system, optimization of the resolution by integrating on-chip micro-shim coils, and further tests on biological samples and also on solid state samples.

Numerous technical difficulties had to be overcome, some of which only became apparent during the course of the project, as for example inhomogeneities of the magnetic field induced by the coil material that has a finite susceptibility. We solved this problem by susceptibility cancelling sandwich layers of the conducting parts and by adding coil extensions. These effects do not occur in standard NMR macrocoils, because of the larger size and further distance to the sample in such a macrocoil.

The work on an alternative material for integration into a microfluidic system could also contribute to the final aim of commercialization of the microcoils, and has been successfully done by our second PhD student. Also, the development of on-chip micro-shim coils for further enhancement of resolution of the NMR spectra could eventually replace expensive macroscopic shim coils in future.

During this project, one PhD thesis has been successfully completed, and a second one is almost finished. We published two research articles on our work, and organized a session of the analytica 2022 conference in Munich, which explicitly dealt with NMR on small sample sizes. In a follow up project, which has been accepted by the Deutsche Forschungsgemeinschaft, we want to use our rolled-up microcoils for the investigation of tiny solid-state samples.

1. Zielerreichung und Umsetzung der Meilensteine

(M1) 12 months: High yield rolled-up micro scale NMR and ESR resonators fabricated on a wafer scale possessing a sufficient quality for resolving relevant features of model materials. Expected duration is 12 months.

M1 was fully achieved regarding self-assembled rolled-up microcoils for NMR. The construction of ESR resonators was no longer pursued, because of the great success with NMR resonators, personal experience with NMR of the first PhD student Piotr Lepucki, and finally because of the departure of Prof. Oliver Schmidt and Dr. Daniil Karnaushenko to Chemnitz in September 2021. However, the IFW is now capable of producing reliable, precise, very well-functioning rolled-up microcoils in high yield. Several materials and geometries were tested in order to increase reliability, performance (in terms of resolution and sensitivity of the NMR signal), ease of the handling and production process, and integration into a microfluidic system.

(M2) 24 months: Compact NMR and ESR hardware set-ups with interfaced resonators. 24 month.

M2 was completed only for the NMR side for the reasons mentioned above. Instead of combined NMR and ESR resonators, which could also interfere with each other regarding additional noise, we concentrated on the optimization of the NMR microcoils. We published two papers (Piotr Lepucki et al. Adv. Mater. Technol. 2021, 6, 2000679 and Journal of Magnetic Resonance 332 (2021) 107077) on our results. Piotr Lepucki finished his PhD thesis in May 2021. He is now working at NMR Service, which was the industrial collaboration partner of our project. The second PhD thesis by Alaleh Mirhajivarzaneh is still ongoing. She is planning to submit her thesis in early summer 2024.

(M3) 36 months: Demonstration of a compact combined NMR-ESR system prototype suitable for commercialization.

As mentioned above, we deviated from our original plan, and did not combine NMR with ESR spectroscopy. Instead, we further improved our NMR microcoils regarding integration into a microfluidic system, optimization of the resolution by integrating on-chip micro-shim coils, and further tests on biological samples and also on solid state samples.

Comparison of accounting: As mentioned above, we financed two PhD students with our project, as planned. We further financed a technician who helped in the production process of the microcoils and who did all necessary preliminary work for a successful roll of the coils. Furthermore, we financed Postdocs, who for example helped in designing micro-shim coils and who calculated and simulated the static field distribution of these coils.

2. Aktivitäten und Hindernisse

During the PhD thesis of Piotr Lepucki, we developed functioning self-assembled rolled-up microcoils, which belong to the smallest NMR coils in the world. No extra capillary is needed, which increases the volume of the sample and therefore the sensitivity. We adjusted several parameters for high resolution of the NMR spectra: we used sandwich layers of Ti-Cu-Ti for the conducting layer of the microcoil in order to compensate the susceptibility of the two materials, which in turn increased the homogeneity of the external magnetic field in the sample space. A polydimethylsiloxane (PDMS) block further increased the homogeneity, and served as a connection to a microfluidic system. The drawback of PDMS was a broad NMR signal that eventually overlaps with the measured NMR signal of the sample. Furthermore, we attached so-called coil extensions to our previous simple roll-up design of the coils in order to further reduce field inhomogeneities, which appear at all edges of structures and therefore also at the edge of the rolled-up coil. Using coil extensions shifts these inhomogeneities away from the sample space.

The PhD thesis of Alaleh Mirhajivarzaneh was at first concerned with finding a suitable replacement for the PDMS block, since PDMS is NMR active as described above. After trying several alternative options such as polymethyl methacrylate, dry film resist lamination, and photopolymer stereolithography, we finally end up with integrating our microcoils into a microfluidic system with an epoxy block. The development of a two-part silicon rubber mold technique to fabricate a microfluidic system for our microcoils was a major step forward from the conventional use of PDMS and soft-lithography towards more large-scale industrial methods such as injection molding.

After that, first experiments with biological fluids and oocytes, and on solid state samples were done. The attempt to get an oocyte into the microcoil failed due to the size of the oocyte. To investigate objects as large as an oocyte, the microcoils need to be modified, and so-called SU8 bars, which control the diameter during the rolling process, need to be removed after the rolling process. This also needs to be done, when using the microcoils for NMR on solid state samples. Another attempt was to measure different concentrations of Na-pyruvate. It is commonly added to cell culture media as an additional source of energy. During metabolomic processes, the concentration of pyruvate changes, and this could be monitored by the intensity of the pyruvate NMR signal. However, the microcoil's detection threshold, which refers to the minimum concentration required to obtain a sufficient signal, is 10 times the standard concentration of Na-pyruvate. Clearly, further improvements of the signal to noise ratio of our microcoils need to be done.

Finally, we developed on-chip micro-shim coils for further enhancement of resolution of the NMR spectra. Up to now, we were able to create planar y-shim coils, and rolled-up x-shim coils, and investigate their impact on the spectral resolution. Shim coils for the z-direction still need to be developed.

Self-assembled rolled-up microcoils are unique, therefore we could not profit of work done on the field from other research groups. We believe that all work that has been performed during the project was necessary and appropriate in order to improve the self-assembled rolled-up microcoils. In the end, we did not achieve all of the goals formulated in the application, but the microcoils developed for NMR are unique and we see a broad future field of applications for these new coils.

3. Ergebnisse und Erfolge

The main outcome of this project are self-assembled rolled-up microcoils for NMR that belong to the smallest NMR coils ever produced. We optimized the performance of these coils so that they can compete in resolution and sensitivity to other commercially available as well as hand-made NMR coils (see Fig. 1).

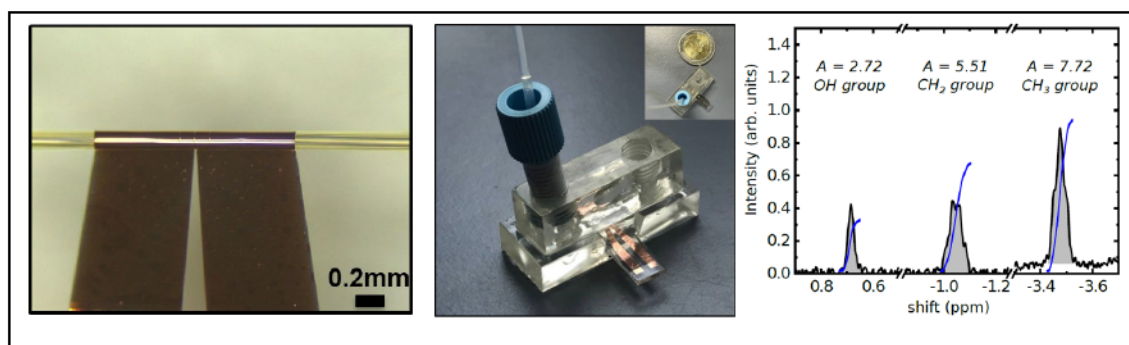


Fig. 1: (a) Self-assembled rolled-up microcoil. The dark part is the Ti-Cu-Ti conducting layer. The transparent tube can be connected to a microfluidic system. The actual coil has a length of about 0.2 mm. The rest of the dark rolled-up structure are so-called coil extensions. (b) Microfluidic system and encapsulation of the microcoil. (c) Single shot ^1H NMR spectrum of 1.5 nl of ethanol $\text{C}_2\text{H}_6\text{O}$ in an unshimmed magnetic field of about 7 Tesla that evidences high resolution and sensitivity of our microcoils. The blue lines are integrals, which correspond to the intensity ratios A , consistent with the number of hydrogens in the different chemical groups (reproduced from Lepucki et al. Adv. Mater. Technol. 2021).

We published two paper (Piotr Lepucki et al. Adv. Mater. Technol. 2021, 6, 2000679 and Journal of Magnetic Resonance 332 (2021) 107077).

We organized a session "Perspectives in small molecule NMR" together with Dr. Roland Hergenröder from Leibniz-Institut für Analytische Wissenschaften (ISAS) in Dortmund on the analytica 2022 conference in Munich, where we presented our results (by Hans-Joachim Grafe). We gave talks on the DPG meeting in Regensburg from 4.9.2022 - 9.9.2022 (by Alaleh Mirhajivarzaneh), at the "biochip" conference in Berlin from 12.6.2022 – 14.6.2022 (by Alaleh Mirhajivarzaneh), and at the conference "Magnetic Resonance on Correlated Electron Materials" in Dresden from 17.9.-23.9.2023 (by Alaleh Mirhajivarzaneh). Earlier participation on conferences and presentation of our results was limited by the Corona epidemic.

Piotr Lepucki finished his PhD thesis in May 2021. He is now working at NMR Service, which is the industrial collaboration partner of our project. Alaleh Mirhajivarzaneh is planning to submit her thesis in early summer 2024.

A follow-up project has been submitted to and accepted by the Deutsche Forschungsgemeinschaft (DFG). In this project, we want to study solid-state samples with our NMR microcoils. The advantage would be that even tiny single crystals could be investigated by

NMR, which was not possible before due to weak signal to noise ratios and marginal filling factors of tiny hand wound coils.

Further publications on the development of micro-shim coils and on the integration of our microcoils into microfluidic systems are planned.

We sent several microcoils to a collaboration partner in the US (Dr. Kayvan R. Keshari, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA). The collaboration is still ongoing.

4. Chancengleichheit, Karriereförderung und Internationalisierung

We funded two PhD students with this project. Piotr Lepucki finished his PhD thesis in May 2021. After that he started to work at our industrial collaboration partner, NMR Service. Alaleh Mirhajivarzaneh is still writing her thesis. She plans to submit it in early summer 2024. The work on the thesis of Piotr Lepucki resulted in two publications, P. Lepucki et al. Adv. Mater. Technol. 2021, 6, 2000679, and Journal of Magnetic Resonance 332 (2021) 107077, where Alaleh Mirhajivarzaneh is a co-author on the first one.

We funded a technician, who supported the students in all technical questions and who prepared the polymers required for the rolling process.

Furthermore, we funded a Postdoc, Adam P. Dioguardi, with this project from 01.03. 2021 until 30.05.2022. He was involved in the project from the beginning on and supports the students with his great knowledge in NMR and programming. To be more specific, besides others, he calculated the magnetic field distribution of the micro-shim coils on the volume of the rolled-up NMR microcoil. Based on these calculations, we identified the optimal design of the micro-shim coils. Another Postdoc in the NMR group, Ranjith Kumar Kizhake Malayil, was funded from 05.05.2022 until 30.06.2023. He continued the work of Adam Dioguardi and helped with his great NMR knowledge to improve the microcoils in sensitivity and to use them for solid state NMR.

Therefore, we can claim without reservation that we have established a well-collaborating, successful research team with equal opportunities concerning gender and internationalization.

5. Strukturen und Kooperationen

Cooperation with Dr. Kayvan R. Keshari, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA.

Very recently after the presentation of our work by Alaleh Mirhajivarzaneh at the conference "Magnetic Resonance on Correlated Electron Materials" in Dresden from 17.9.-23.9.2023, Prof. Dr. Nicholas Curro asked for our rolled-up microcoils. He wants to use them for solid state NMR on crystals, which have been shaped by focused ion beam (FIB).

We organized a session "Perspectives in small molecule NMR" together with Dr. Roland Hergenröder from Leibniz-Institut für Analytische Wissenschaften (ISAS) in Dortmund on the analytica 2022 conference in Munich, where we could also present our results to a broad audience.

The departure of Prof. Oliver Schmidt and Daniil Karnaushenko to Chemnitz changed the Governance of our project substantially. This might have lead to a certain delay in the project and to a change in focus from liquid-state NMR to solid-state NMR, for which we also applied successfully for a DFG research project.

6. Qualitätssicherung

Good scientific practice is a major concern of the IFW Dresden and is exemplified daily by the scientific board. One of the publications has been made open access, Journal of Magnetic Resonance 332 (2021) 107077. No animal testing has been conducted.

7. Zusätzliche Ressourcen

The IFW Dresden provides a clean room, where most of the fabrication of the microcoils take place. The NMR lab is also provided by the IFW, where most of the NMR measurements have been done. Furthermore, the NMR experiments in a chemical grade, high resolution NMR spectrometer at 11.78 Tesla have been done in another IFW lab, lead by Dr. Alexey Popov. Also, we send several microcoils to our new collaboration partner at the Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA, where further NMR measurements have been done by the PhD students Thasin Peyear and Thomas Ruan and their supervisor Kayvan Keshari.

As an example, IFW Dresden has invested around 20.000,- Euro in 2021 in the NMR lab in new equipment, consumables, and repair.

All internal IFW cooperation partners (Dr. Hans-Joachim Grafe, Dr. Vladislav Kataev, Dr. Daniil Karnaushenko, the last two only in the first year, since we discard ESR (Kataev) and since Dr. Karnaushenko left to Chemnitz) contributed in the daily work by guiding the PhD students and instructing the technician.

8. Ausblick

Miniaturization is a key technological approach in current times. This also applies to miniaturization of detectors: to make them portable, to make them integrable into multi-functional systems or to enable detection of smaller amounts of samples. However, miniaturization in NMR is not yet as advanced as in other measurement techniques. We believe that we have taken a good step towards the miniaturization of NMR with our microcoils. We will further produce these coils and investigate various kinds of samples. We will continue the collaboration with our US partner and will also make the coils available to other NMR groups. In future, we will concentrate on the investigation of solid-state samples with these microcoils, which should open up new experiments on samples that could not be investigated by NMR so far.