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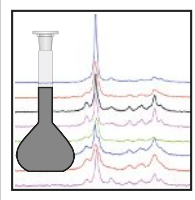

# Highlights of Analytical Sciences in Switzerland

## Division of Analytical Sciences

A Division of the Swiss Chemical Society

## CMOS and 3D Printing for NMR Spectroscopy at the Single Embryo Scale

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Nuclear magnetic resonance (NMR) allows, among many other applications, for non-invasive studies of intact living entities. In particular, NMR is successfully employed for imaging and to obtain detailed information on the chemical composition of large living animals. NMR experiments at the volume-scale of single microorganisms and single cells are hindered by the limited sensitivity of the detector and the difficulties in positioning such small samples in proximity of the detector. Many interesting biological entities (*e.g.* the human ovum and those of other mammalians) have typical volumes below 1 nL. Commercial NMR probes have a too low sensitivity for the investigation of such small important entities.

Recently, we introduced an innovative generation of NMR probes, based on the combination of single-chip CMOS integrated electronics together with high-resolution 3D printed microfluidic structures. The CMOS technology is used to implement miniaturized probes, where a multilayer microcoil is co-integrated on the same chip with the transceiver electronics. The microfluidic structures are fabricated using a two-photon polymerization 3D printing technique having a resolution better than 1 $\mu m^3$. The adopted 3D printing approach allows to fabricate complex microfluidic structures tailored to position and feed biological samples in the most sensitive region of the CMOS-integrated microcoil. Using a probe having a sensing volume of 200 pL and a sensitivity of $2\times10^{13}$ spins/$Hz^{1/2}$, we demonstrated direct reading of endogenous compounds in sub-nL eggs of microorganisms and in sub-sections of worms. In the figures we report spectra of body sections and eggs of small animals (which show differences among species and heterogeneities among individuals) and of a test liquid solution (which demonstrates a spectral resolution of 2 Hz). **The proposed combination of CMOS and 3D printing technologies achieves state-of-the-art sensitivity for the NMR studies of nanoliter and subnanoliter living biological entities.**

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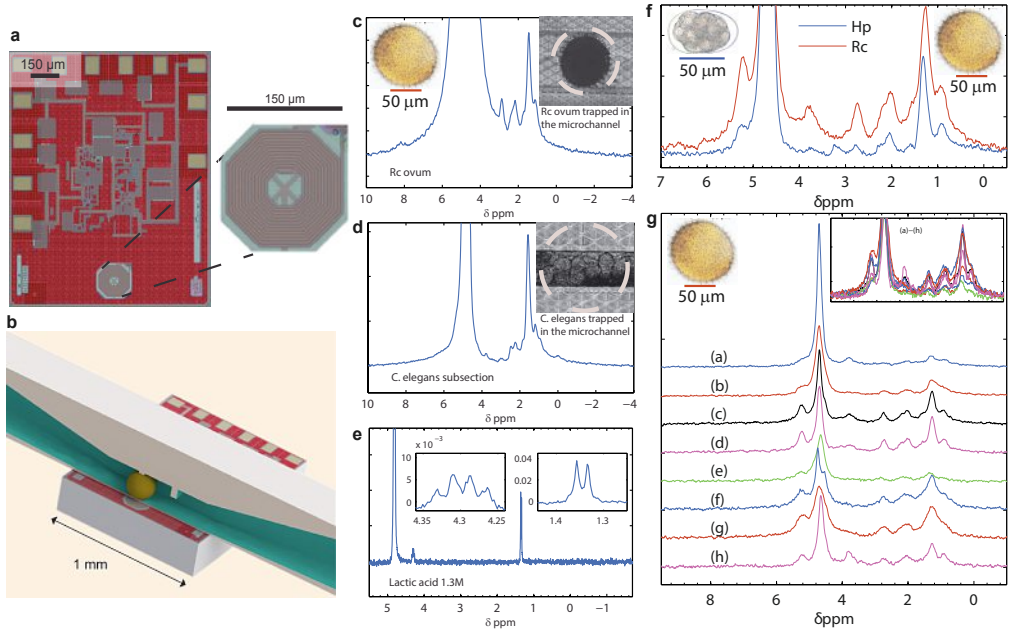


Fig. 1. (a) Single-chip CMOS transceiver with co-integrated microcoil, and (b) assembled with a 3D printed microchannel. (c) $^1$H NMR spectrum of a single tardigrade ovum, belonging to *Richtersius coronifer* (Rc), in $H_2O$. (d) $^1$H NMR spectrum of an intact *Caenorhabditis elegans* worm subsection in PBS. (e) $^1$H NMR spectrum of 1.3 M lactic acid in $H_2O$. (f) $^1$H NMR spectra of single sub-nL ova (*Richtersius coronifer* (Rc) and the parasitic nematode *Heligmosomoides polygyrus bakeri* (Hp)). (g)$^1$H NMR spectra of eight, visually identical, Rc ova in $D_2O$.

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