CMOS based sensors for micro-NMR
Magnetic Resonance at the Embryo Scale

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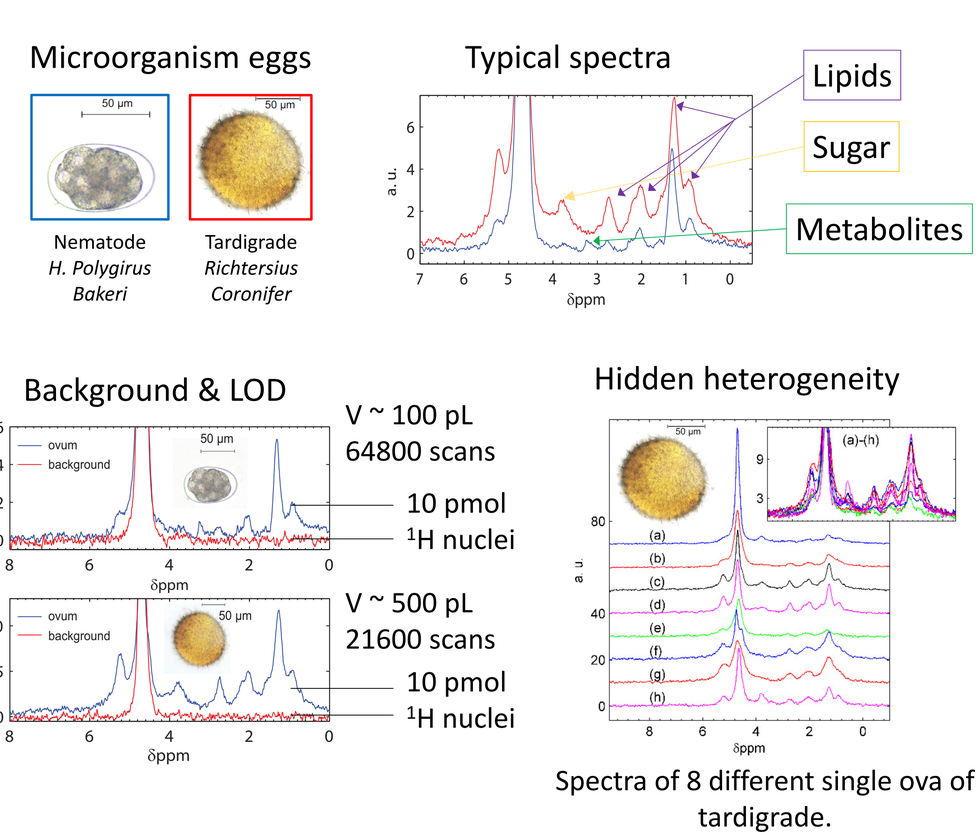
CMOS technologies define a new standard for micro-NMR. A user-friendly and robust solution for in-vivo measurement of micro-tissues and embryos was recently implemented.

Preliminary observations

Many interesting biological entities (e.g., the human embryo) have typical volumes below 1 nL. The commercially available NMR devices are insufficient for the investigation of such small but important samples. Conventional micro-coil technology has significant limitations: parasitic sensing regions negatively impact SNR and limit further miniaturization, difficult sample handling makes them available only to highly trained personnel, high production costs limit widespread use.
Recently, we introduced CMOS-based NMR probes overcoming at once all these issues, and demonstrating a superior degree of versatility combined with cutting-edge sensing performance. CMOS probes, where multilayer micro-coils are co-integrated on the same chip with the transceiver electronics, deliver state-of-art performance in volumes ranging from 10 nL down to 100 pL. Overall, they set a new standard for micro-NMR.

Feature / Probe type	Local sensing	High resolution	Scalable manufacturing	Extendable to arrays	Broadband operation
Solenoid	×	×	×	×	×
Microslot	×	×	×	×	×
Planar microcoil	×	√	√	×	×
CMOS probes	√	√	√	√	√

With a CMOS probe having a sensing region of about 200 pL and a spin sensitivity of $1.5*10^{13}$ spins/$Hz^{1/2}$ at 7 T [1,2] we demonstrated direct reading of endogenous compounds in sub-nL eggs of microorganisms [2,3], high resolution spectroscopy in liquids (0.01 ppm), and in-vivo spectroscopy of tardigrade eggs and sub-sections of intact C. elegans worms immersed in liquids. This last result was obtained by combining CMOS probes with 3D direct laser writing techniques [4].

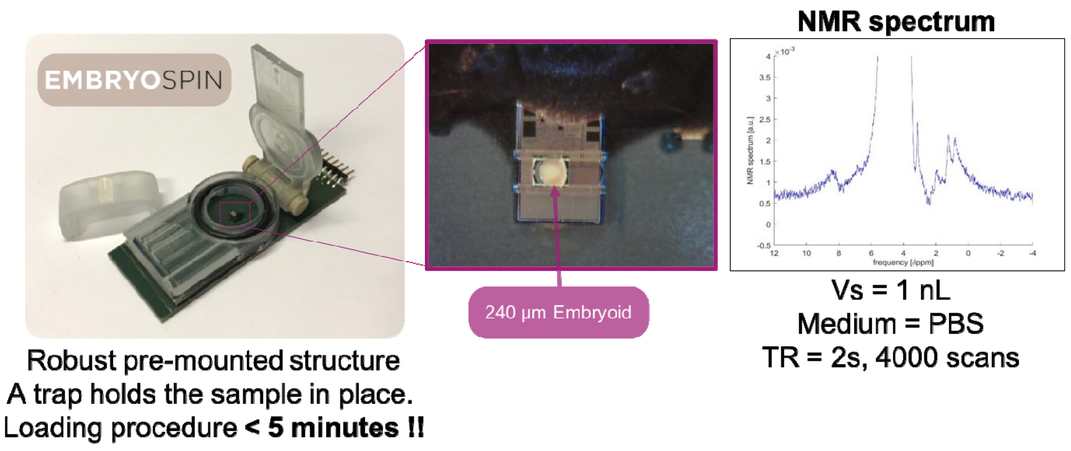


Spectra of 8 different single ova of tardigrade.

EmbryoSpin sensors

Starting from our preliminary observations, we have now developed a packaged solution that contains all the advantages of CMOS probes in a user-friendly robust device. This new technology, named EmbryoSpin, consists of a sensor having the size of a microscope slide. A microsystem is constructed on a printed circuit board, where a CMOS chip is combined with a 3D printed micro-structure that enables many possible custom solutions for sample handling. In the picture below we can see an EmbryoSpin sensor, consisting of an enclosure to contain a medium of choice in which the sample is immersed, a plug&play interface, and a micro-NMR system that can work in contact with liquids.

EmbryoSpin is based on improved CMOS sensors that target a volume of about 2 nL with a spin sensitivity of $2*10^{13}$ spins/$Hz^{1/2}$ at 7 T. With these microchips we can measure about 10 times faster than previously achieved at parity of concentration sensitivity in the sample region. The design is optimized to work broadband from 200 MHz up to 1 GHz. To demonstrate the power of detection of our probe we recently tested it on embryoids obtained from murine stem cells. This measurement, obtained in less than 3 hours, shows prominent signals corresponding to lipids and metabolites. This is the first NMR measurement on a stem-cell embryoid.

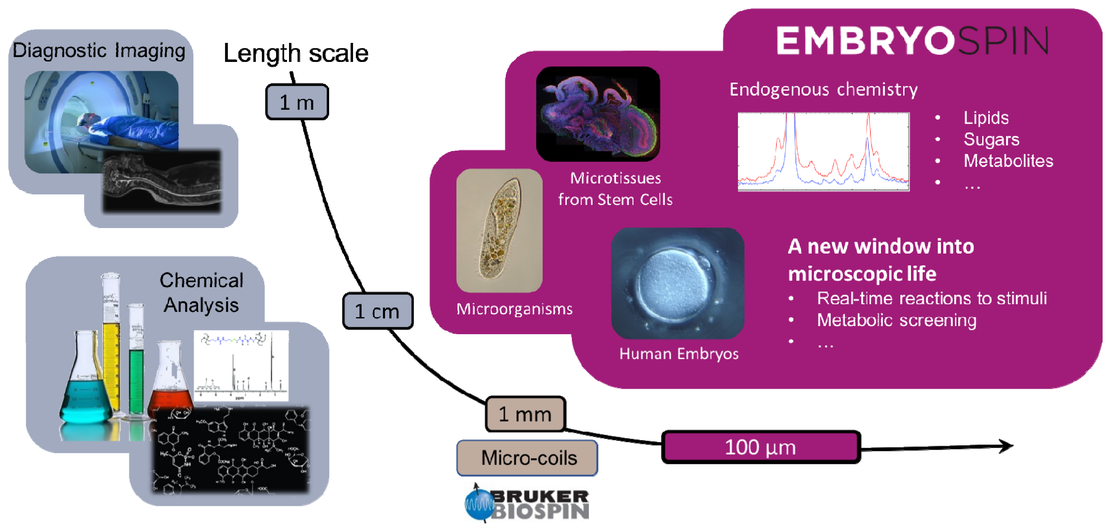


Robust pre-mounted structure
A trap holds the sample in place.
Loading procedure **< 5 minutes !!**

Vs = 1 nL
Medium = PBS
TR = 2s, 4000 scans

Outlook

EmbryoSpin sensors finally enable NMR on samples that are currently out of reach for the NMR community, such as large unicellular microorganisms, stem-cell micro-tissues, and even human embryos. Such technology promises novel applications as well as potential new markets for magnetic resonance.



[1] M. Grisi, at al. Review of Scientific Instruments, 2015, 86, 044703.
[2] M. Grisi, et al. 58th Experimental Nuclear Magnetic Resonance Conference, ENC 2017.
[3] M. Grisi, et al. Scientific Reports, 2017.
[4] E. Montinaro, M. Grisi, et al. PlosOne, 2018.

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