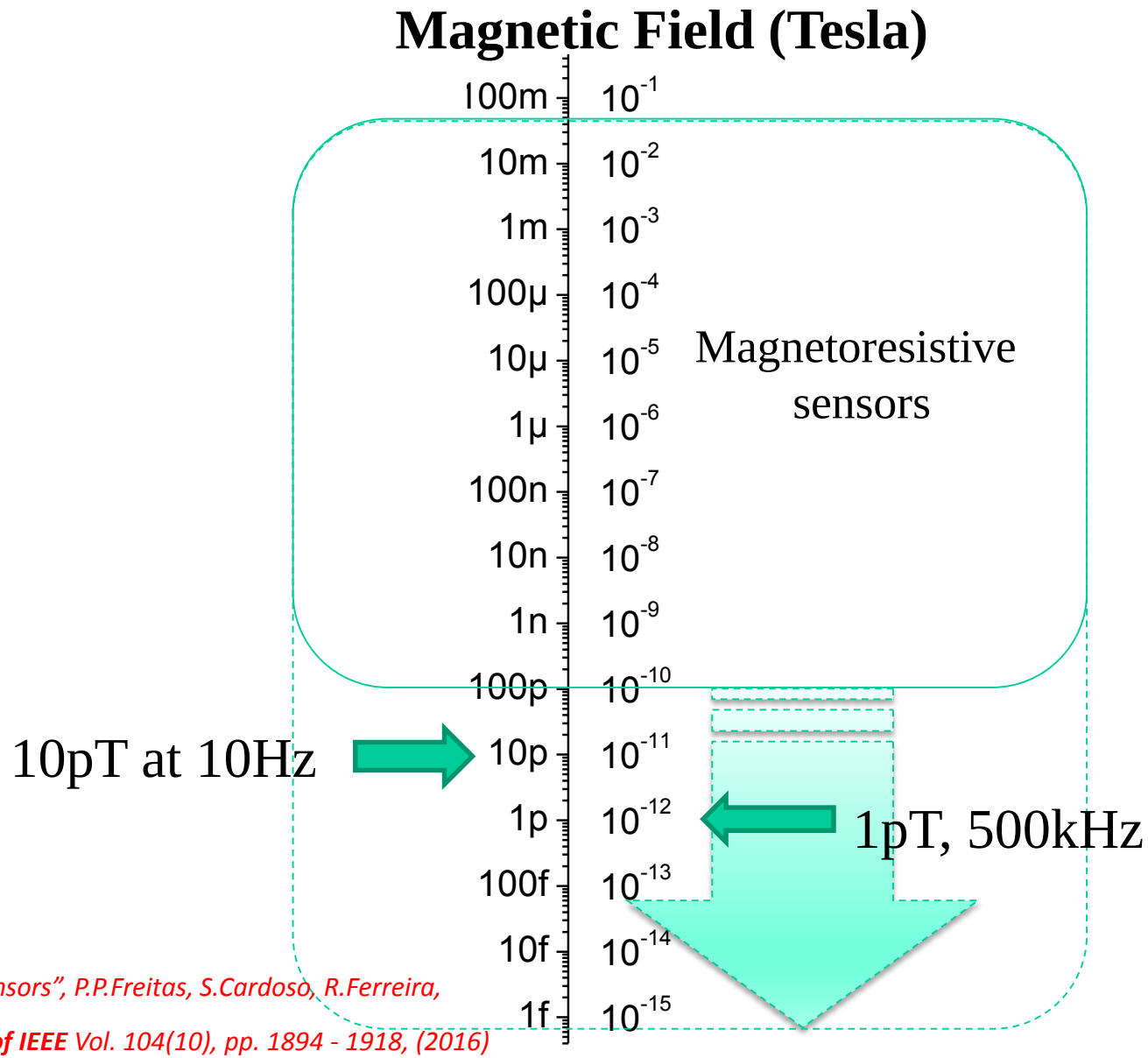
Pushing towards 1pT at 1Hz , and 1fT at high f

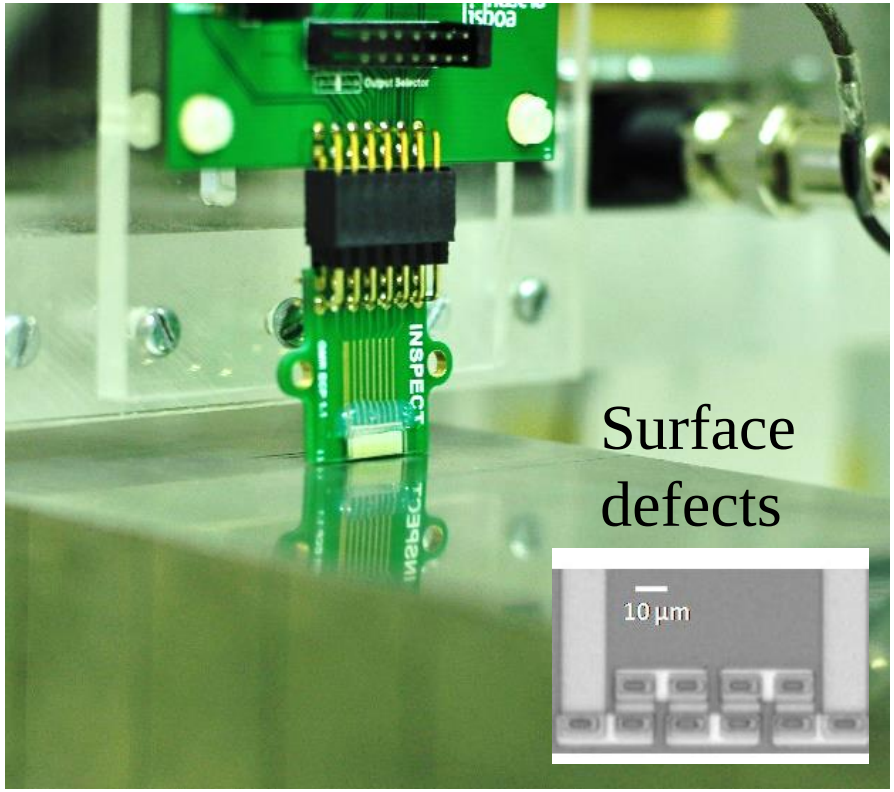


"Spintronic Sensors", P.P.Freitas, S.Cardoso, R.Ferreira,

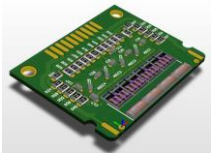
***Proceedings of IEEE** Vol. 104(10), pp. 1894 - 1918, (2016)*

NDT Testing with TMR sensors

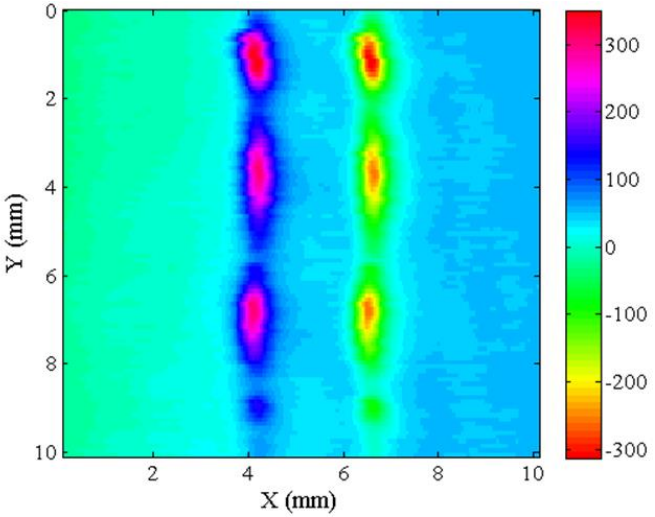
In collaboration with INESC ID, CEA

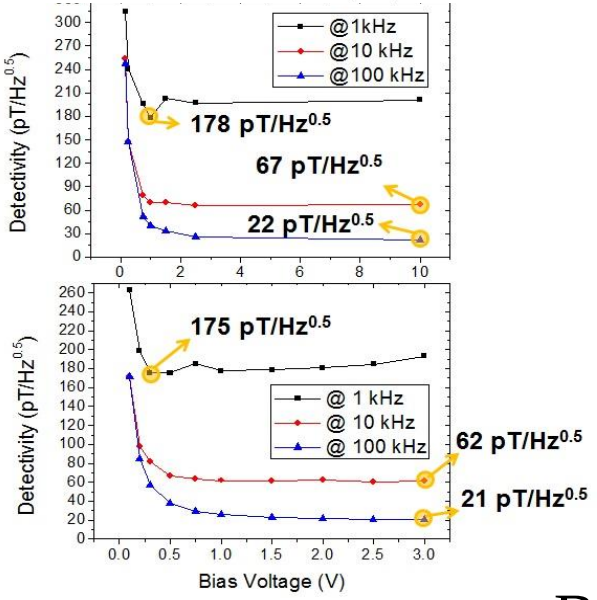


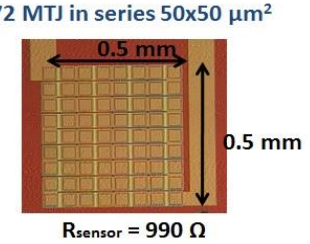
Aluminum Mock-up with defects with a width of 100 µm and a depth ranging of 0.2, 0.5 and 1 mm

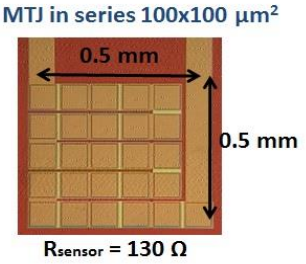


Final prototypes:
TMR sensors, current lines, ASICS







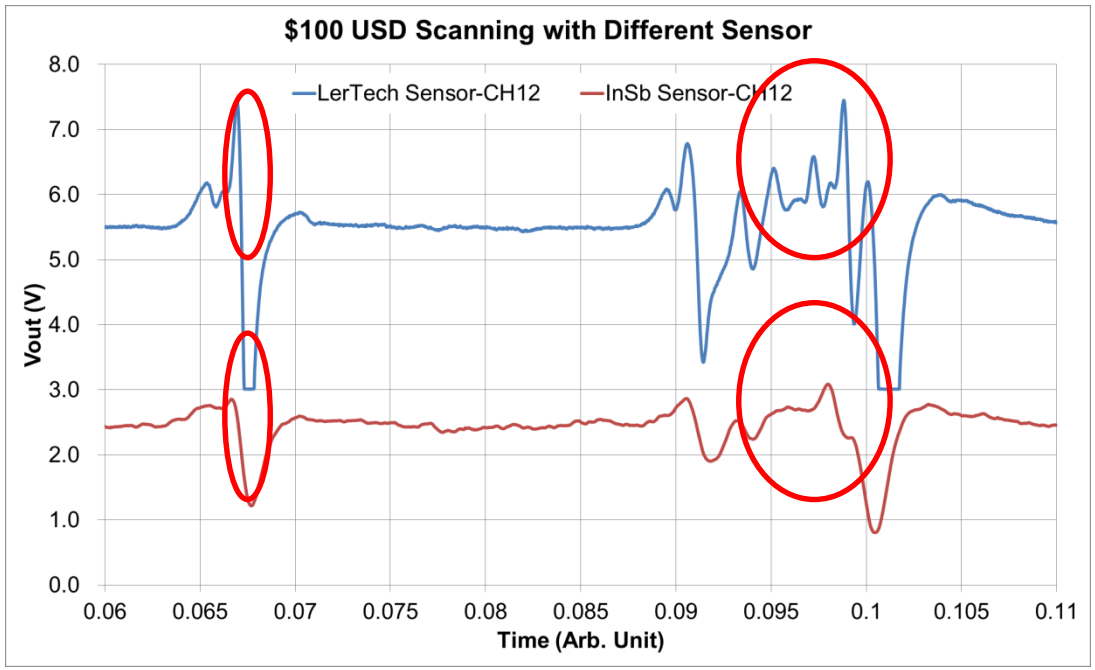


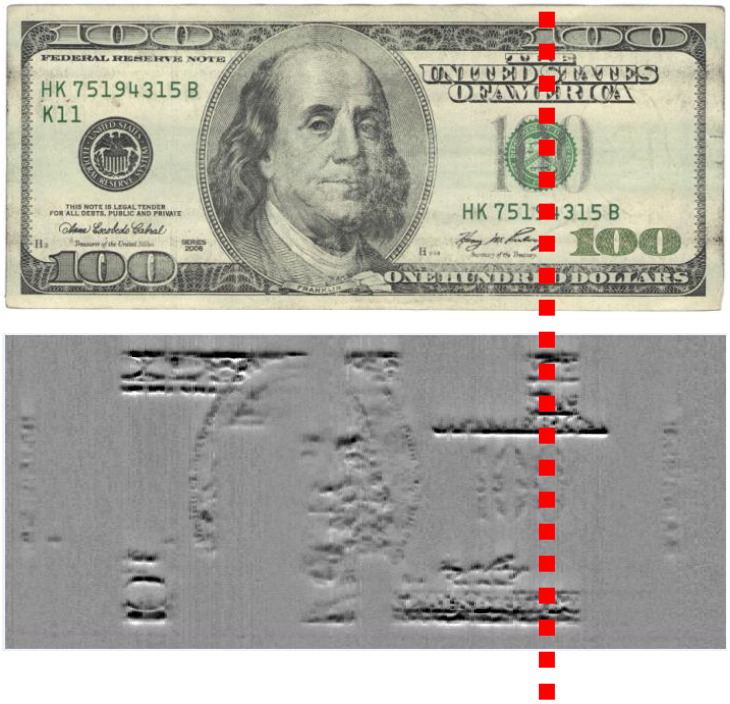
Buried defects

INESC-MN

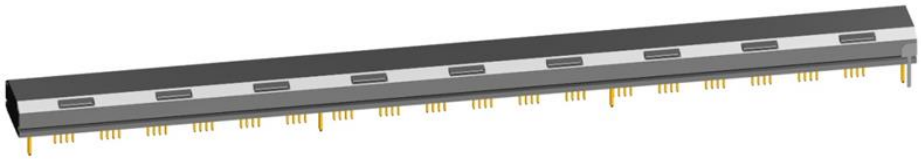
Scanning probes IV

Sold to spanish MINT, and several others

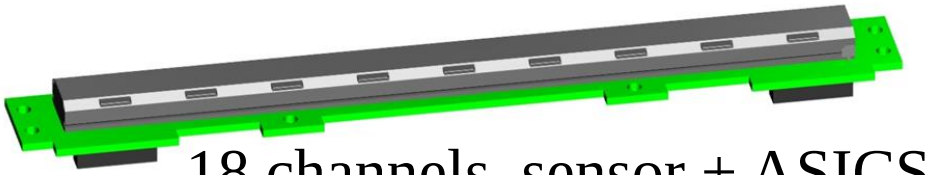




LerTech/Simomags Sensor shows higher spatial resolution then InSb Sensor.

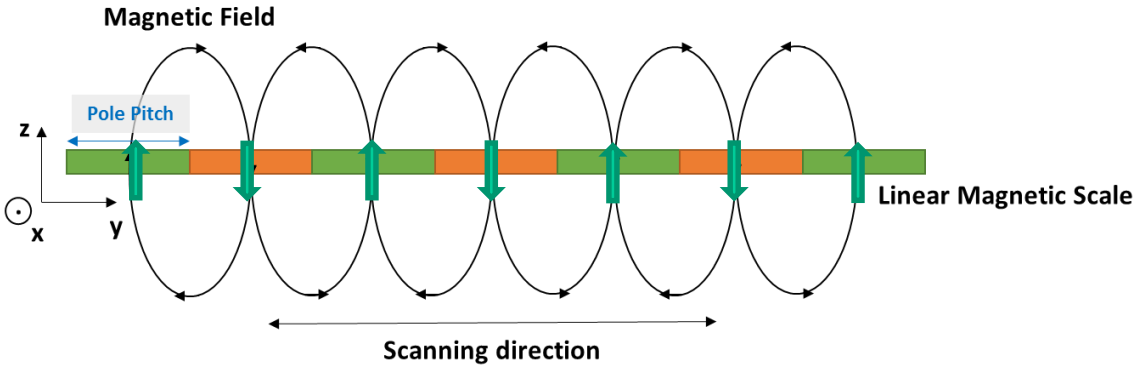


18 channels, sensor only

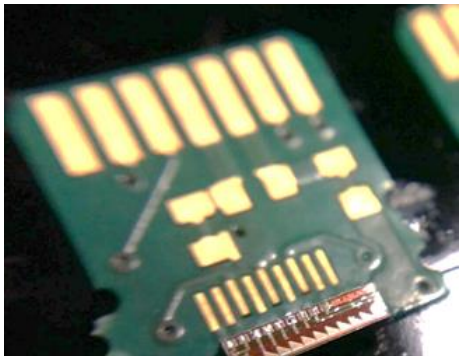


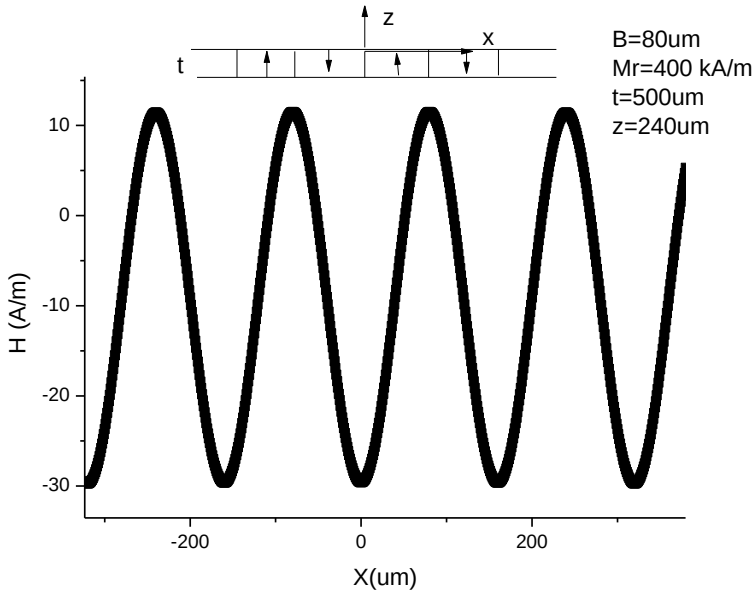
18 channels, sensor + ASICS

Scanning Probes II: Linear Encoders

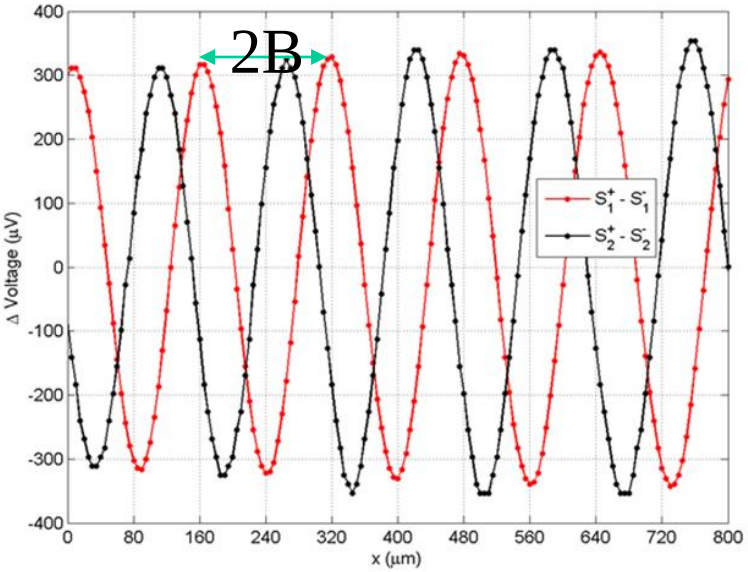


Magnetic field distribution of a linear magnetic scale with an out of plane magnetization.





Calculated Hz

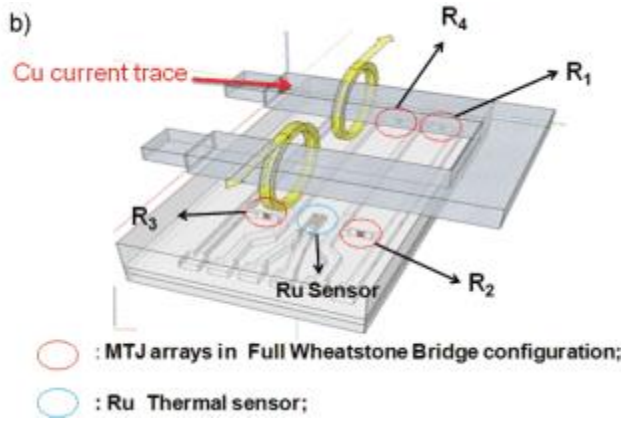


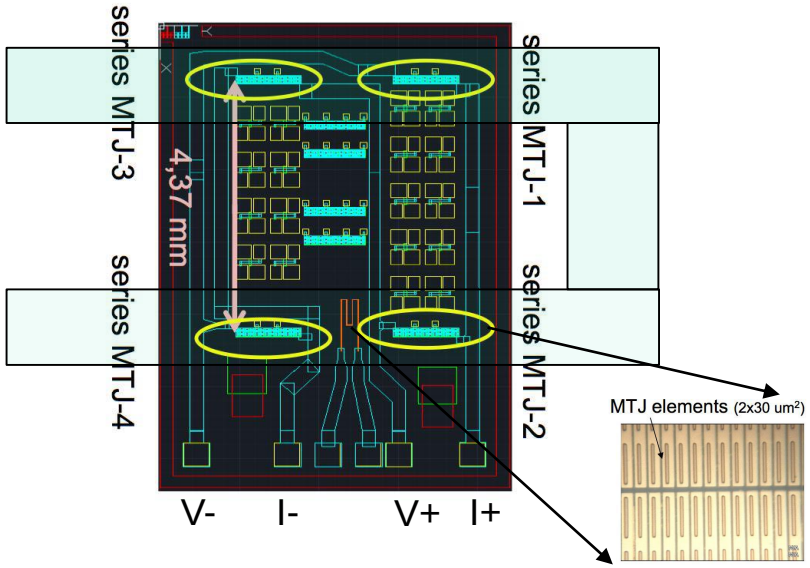
sin-cos output obtained at INESC-MN during a scan along 800 um at a distance of 150 um from the scale.

Current sensor / Powermeter

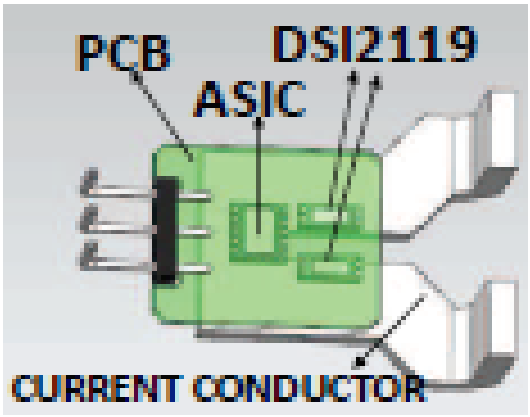
Sensor architecture: open loop, coreless, U shape Cu strip on PCB

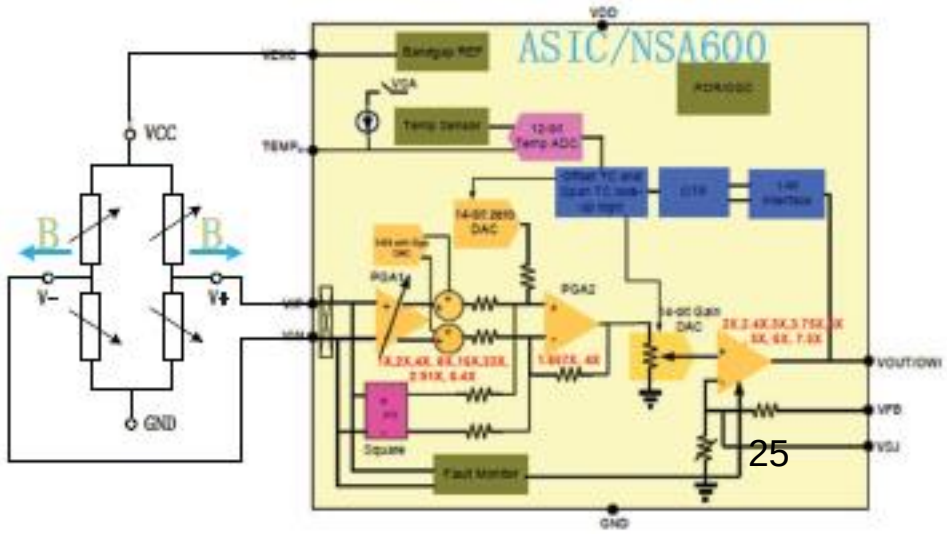
Single TMR chip, integrated temp sensor analog multiplier





Dual TMR +ASIC





1-Scalable magnetoresistive biochips for point of care diagnostics

Labelled targets

DNA targets

Magnetic labels

Hybridize first
Label after

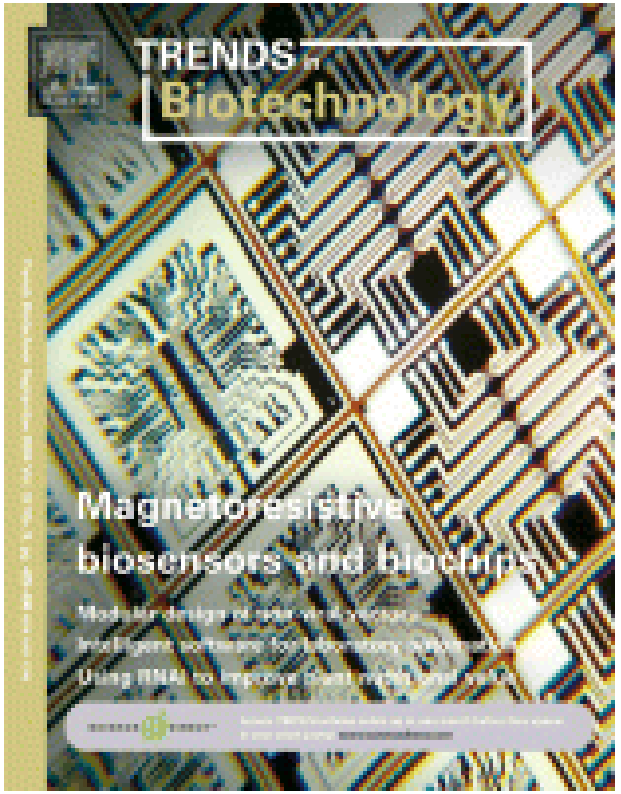
DNA probes

Passivation

Substrate

Spintronic transducer

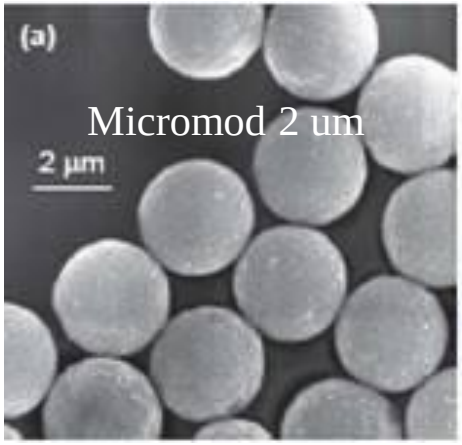
Hybridization of DNA probe and target

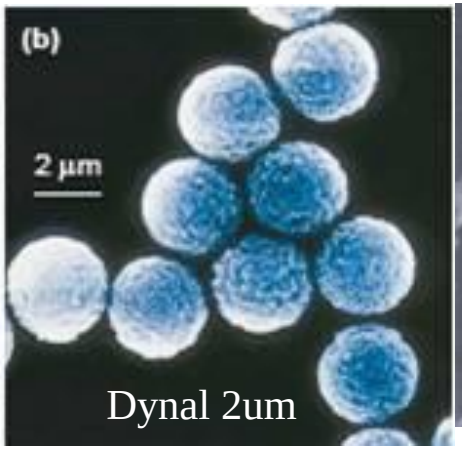


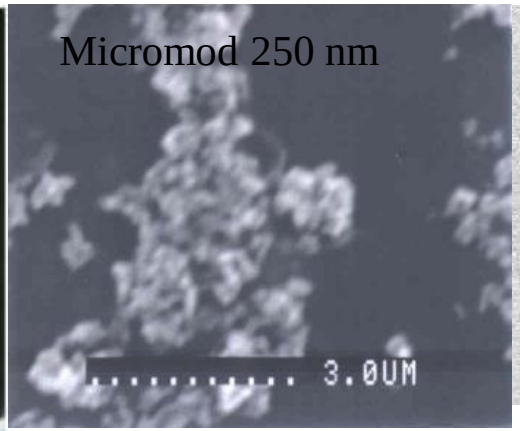
Trends in Biotechnology, August 2004; ACS Nano Perspectives10.1021, 2017

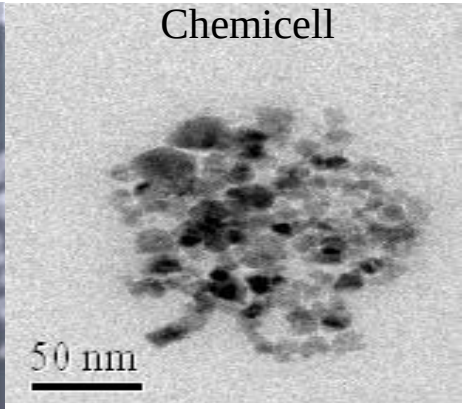
1 a) magnetic labels

Particles typically used in bio-separation



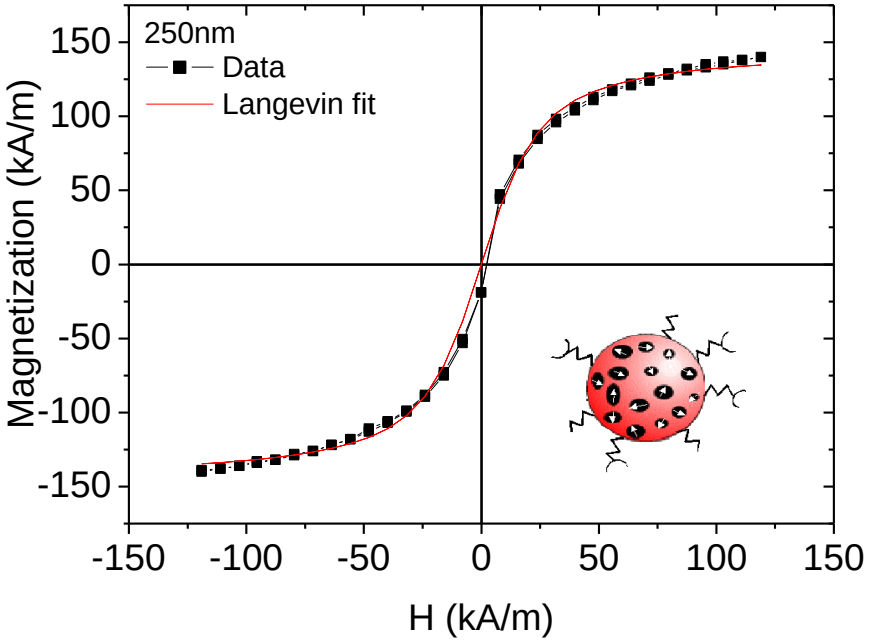






Micromod, Germany http://www.micromod.de

Dynal Biotech, Norway http://www.invitrogen.com



ADVANTAGES

- Non remanent magnetic moment (avoid clustering)
- High saturation moment (high signals)
- Small (avoid steric hindrance)
- Stable
- Biocompatible

Lowest fields to be detected

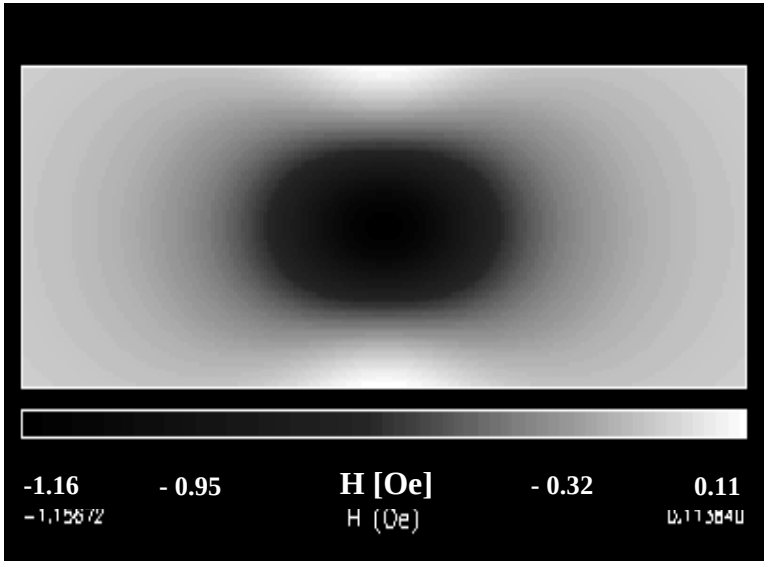
For a 50nm FeOx particle:

χ=0.7, H=1.2kA/m, d=0.2um

B^{max}=4μT

But for a 6μm^2 sensor,

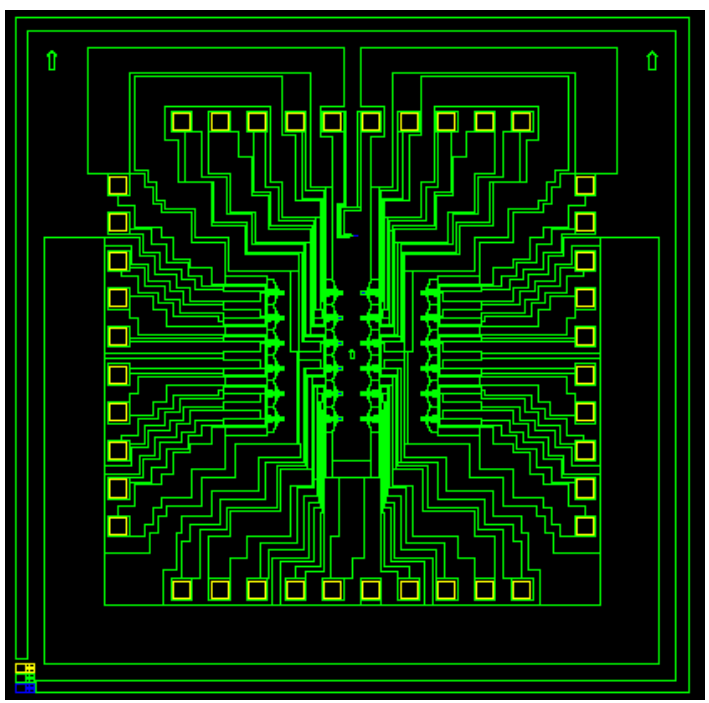
B_{aver} = 1 nT

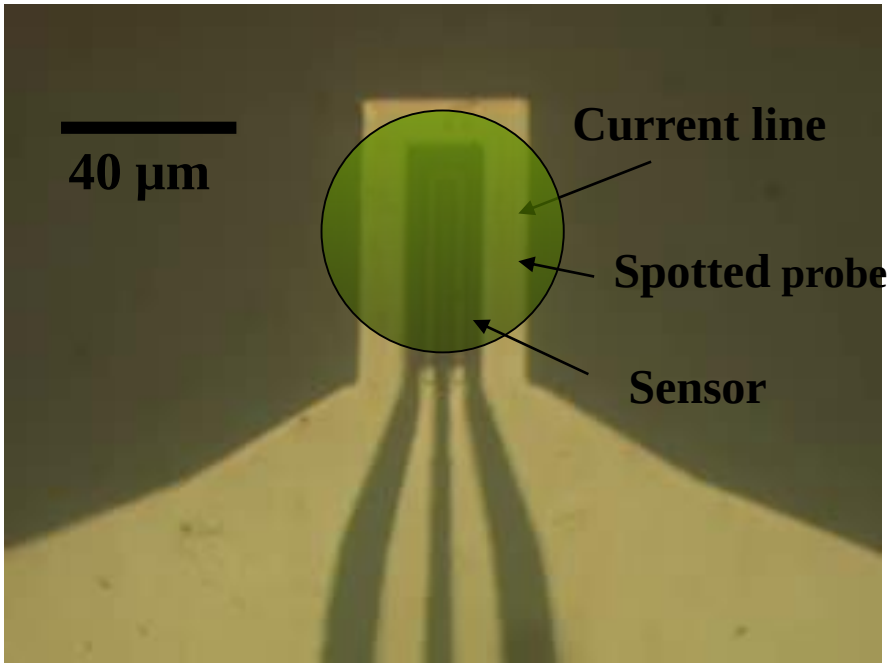


HOW TO DETECT THESE FIELDS?

Magneto encephalography, B 10fT (SQUIDS, SVs+SC FG)
Magneto cardiography, B few pT
MR Biochips, few nT

INESC-MN's 3rd generation MR biochip





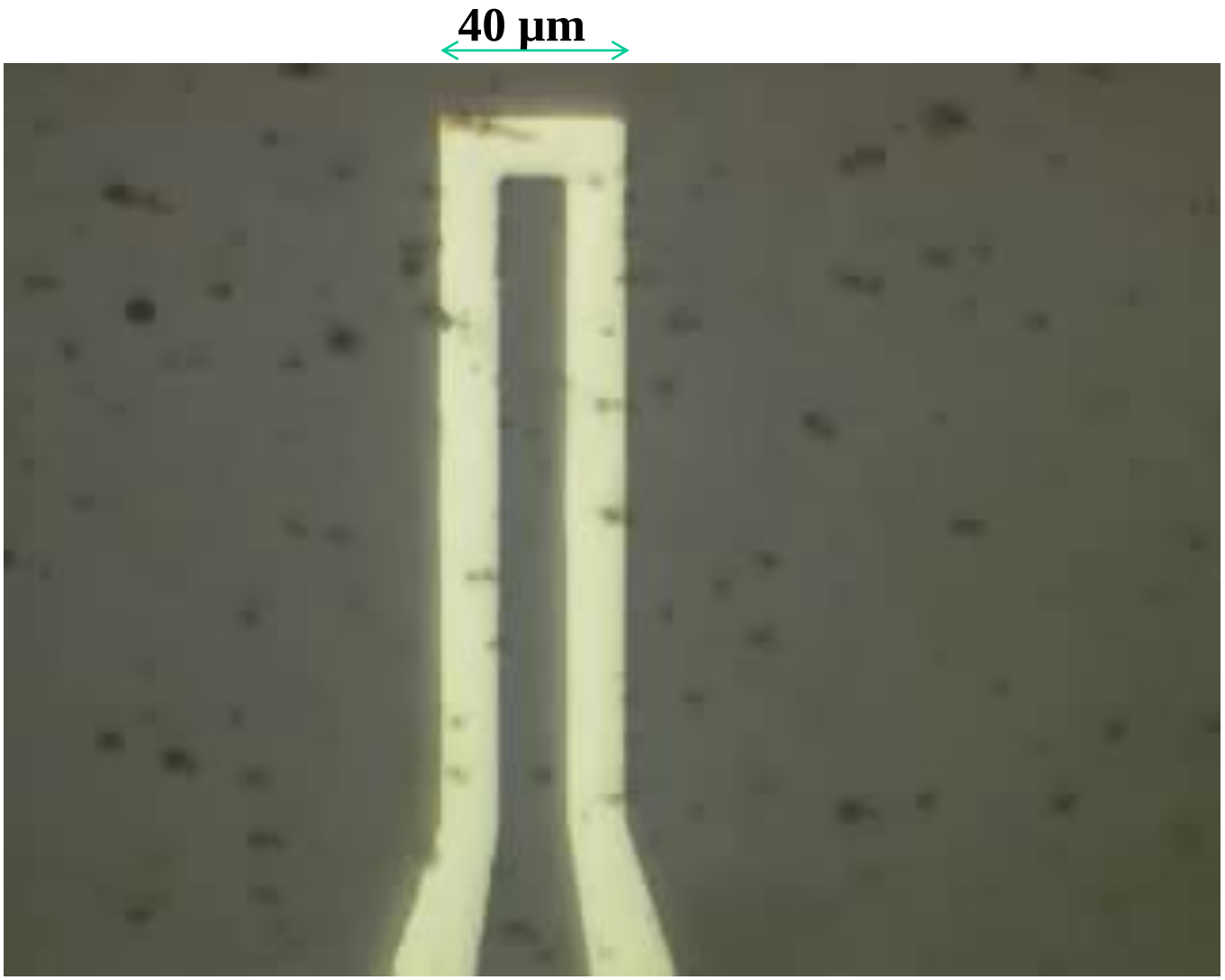
- 24 sensing units:
  - 1 U-shaped spin-valve sensor (2.5 µm × 80 µm)
  - 1 U-shaped current line (l = 50 µm; w = 10 µm; s = 17 µm)
- 1 single sensor (2.5 µm × 80 µm)

→
- **Higher dynamic range**
- **Higher biological sensitivity**
- **Need to focus labels in large areas (1000-2000 µm²)**

←

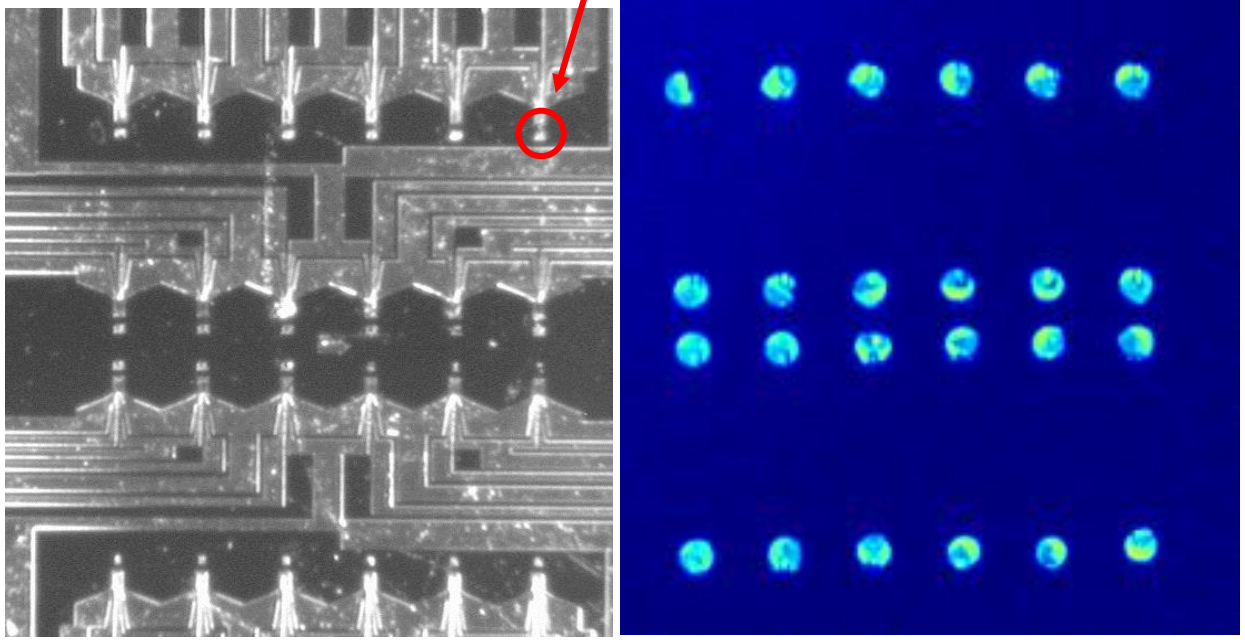
Appl.Phys.Lett., vol.87, pp.013901, 2005

1-e) target arraying over immobilized probes: 250nm beads and magnetically assysted hybridization

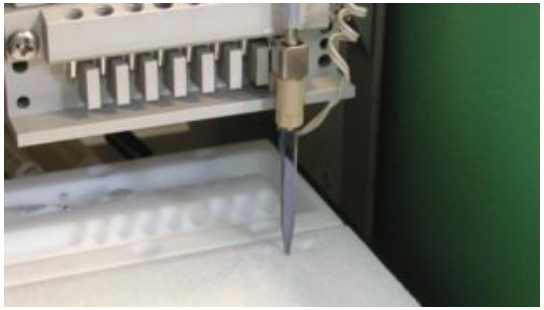


1-d) Spotting biological targets on the biosensing platform

Spotting site



1 μM Oligo solution, Cy5 labeled
200 pL droplets



Gesim spotter

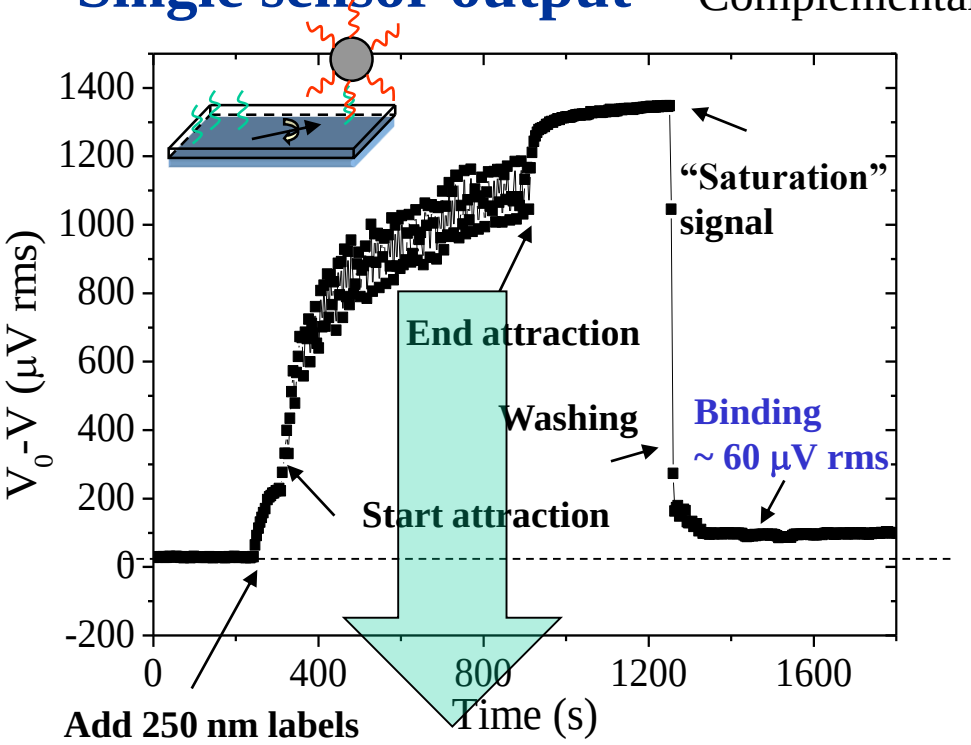
Disposable biochip

Biomolecular recognition experiments

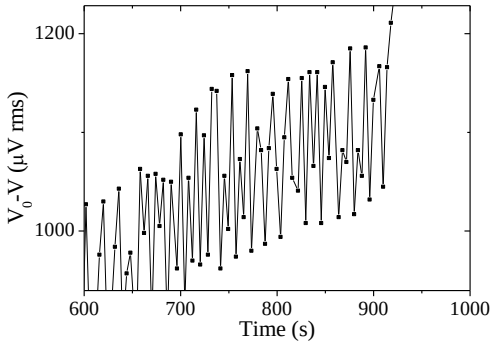
Cystic Fibrosis Related DNA hybridization

Single sensor output

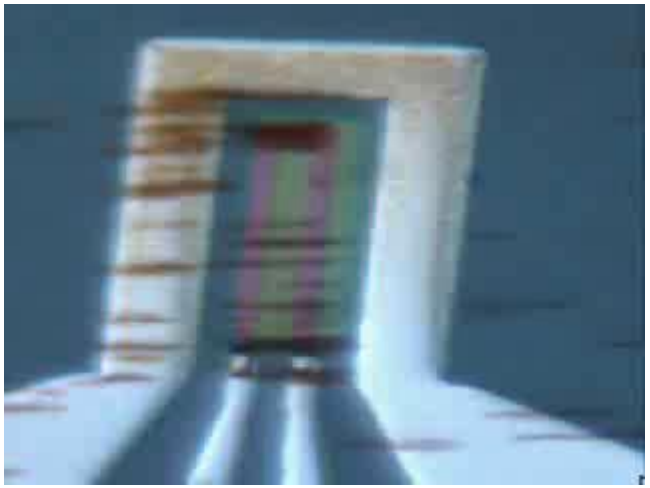
Complementary target

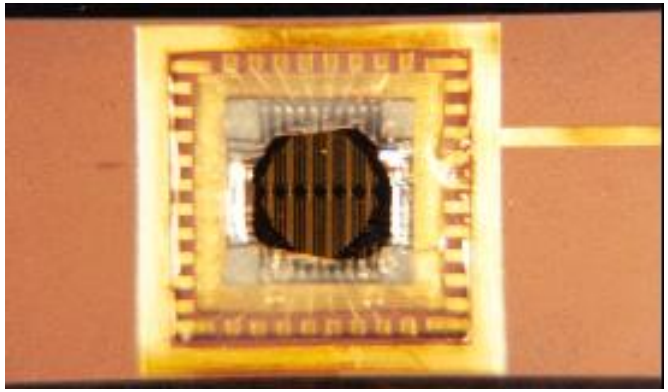


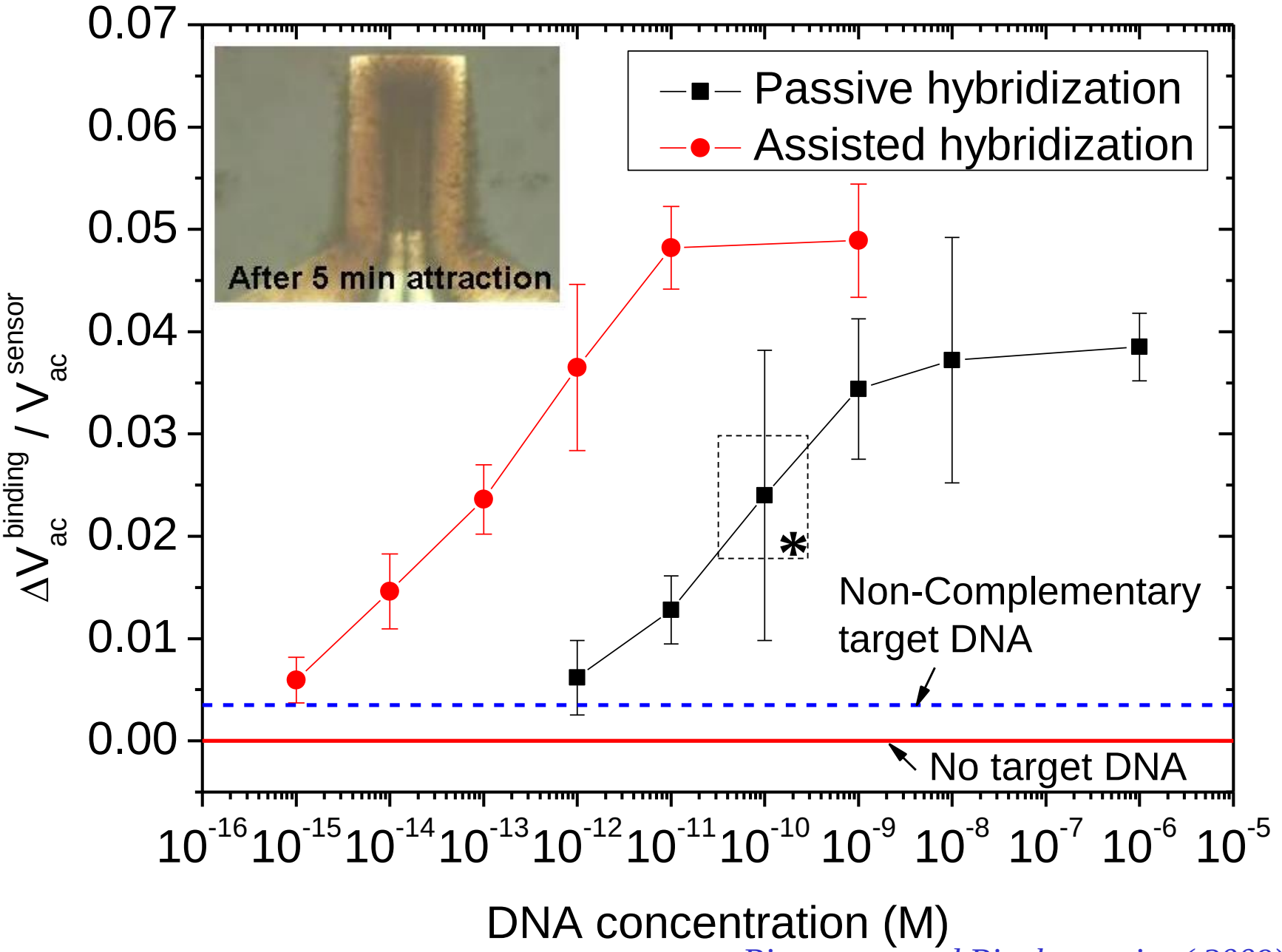
Add 250 nm labels



Dynamic hybridization at work







Biosensors and Bioelectronics (2009)

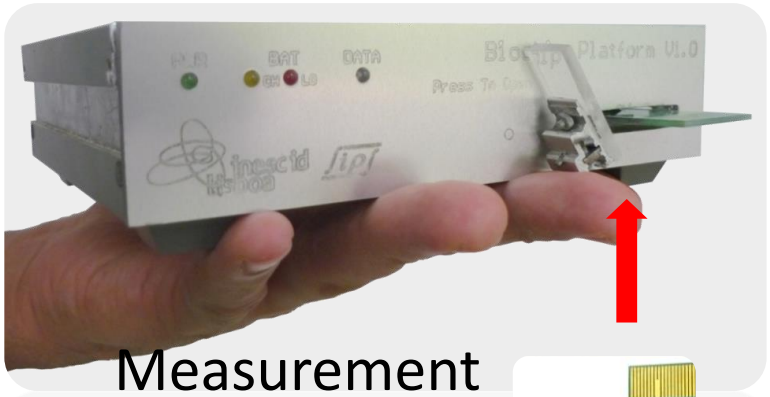
INESC MN – INESC ID technology

MR biochip static platform

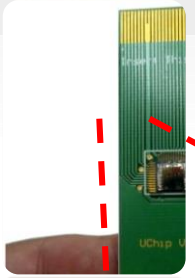
Develloped at INESC MN and INESC ID 2000-2013

Licensed to Magnonics, 2014

Patents pending (3)



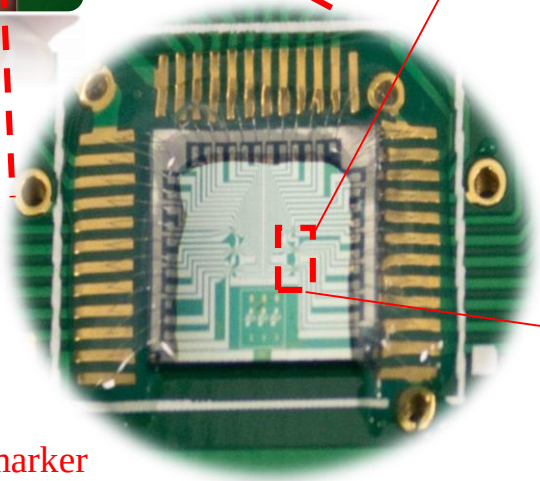
Measurement platform



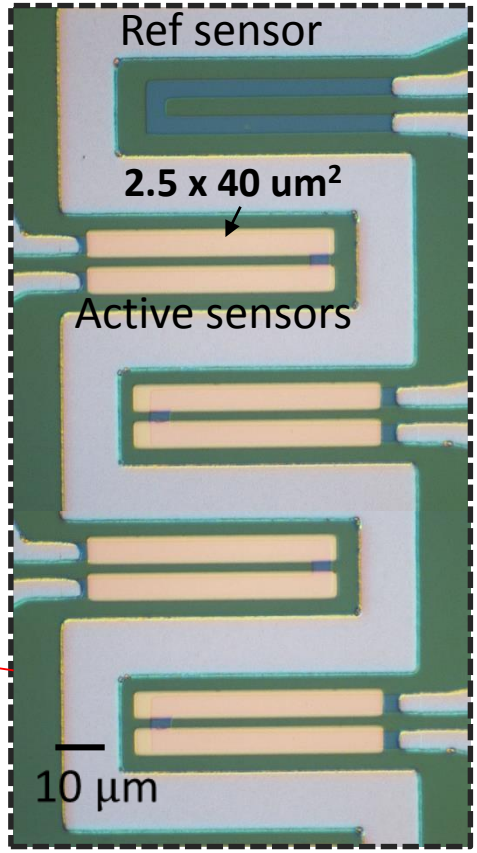
MR biochip

- 30 sensing units
- 6 groups of
- 5 sensors

(4 bio-active + 1 reference)



Chip area: 6 x 7.2 mm^2



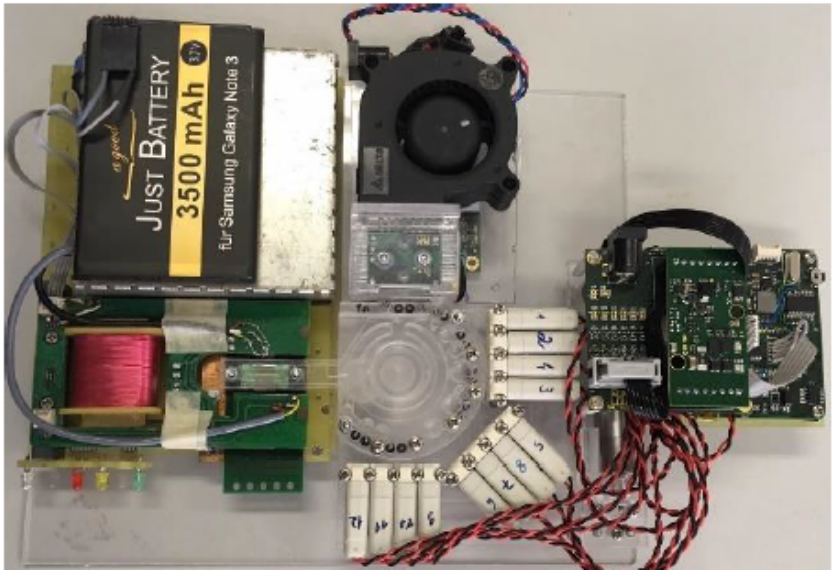
Application:

Protein chip: brain eschemia biomarker detection

DNA chip: cell free DNA detection as cancer biomarker

With MAGNOMICS today: detecting bacteria in milk from mastictic cows

High sensitivity and **ability to provide specific responses** to biological questions: not just the pathogens, but also may inform as to the best antibiotic to use for treatment	**Fast results** turnover time (4 hours) in an **all in one compact platform**, bringing the laboratory methods to the farms	**Multiplexability** and **flexibility**: adaptable to a number of different applications, able to detect several types of molecules/set of bacteria simultaneously	**Portability** (hand-held device), **long autonomy**, **easy to use** (one-step/one-button) and **low price** compared to similar solutions



PRODUCT
- Reader plus disposable cartridge
- Approx. €20 end user price per cartridge (margin 40%)
- First product will be a "cow side" bovine mastitis test

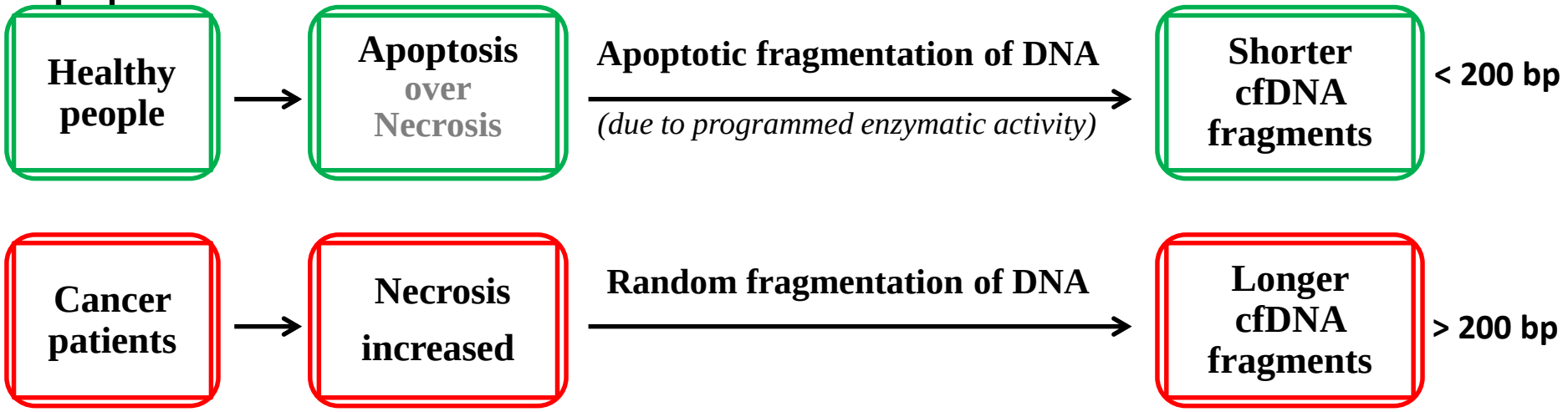
READER
- Basic signal acquisition and processing
- Connects to PC or mobile phone
- Can be leased or offered

CARTRIDGE
- Disposable cartridge, including sample processing, PCR amplification and dozens of DNA sensors
- Customized detection capability
- Sold in large volumes

Application: Cell-free DNA as cancer biomarker?

- **Cell-free DNA:** DNA that can be found outside of cells in blood circulation. Results mainly from dying cells (apoptosis or necrosis)

- **The cfDNA found in cancer patients is qualitatively different from what is found in healthy people:**



Integrity index:ratio $\frac{\textbf{ALU247}\ \textit{(longer cfDNA fragment)}}{\textbf{ALU115}\ \textit{(shorter cfDNA fragment)}}$

Universal cancer biomarker in therapy follow-up ?

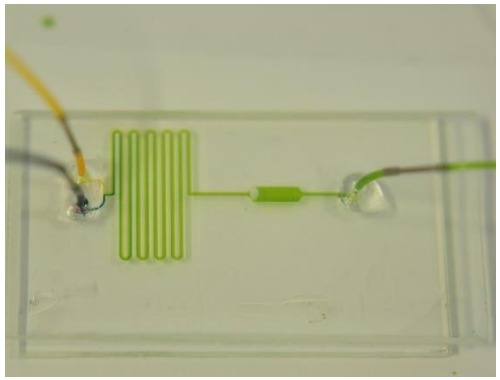
1-Blood finger-prick

Healthy donors

1,2-DNA extraction from Plasma by comercial kit or

3-MNP labelling and

4-Magnetic separation



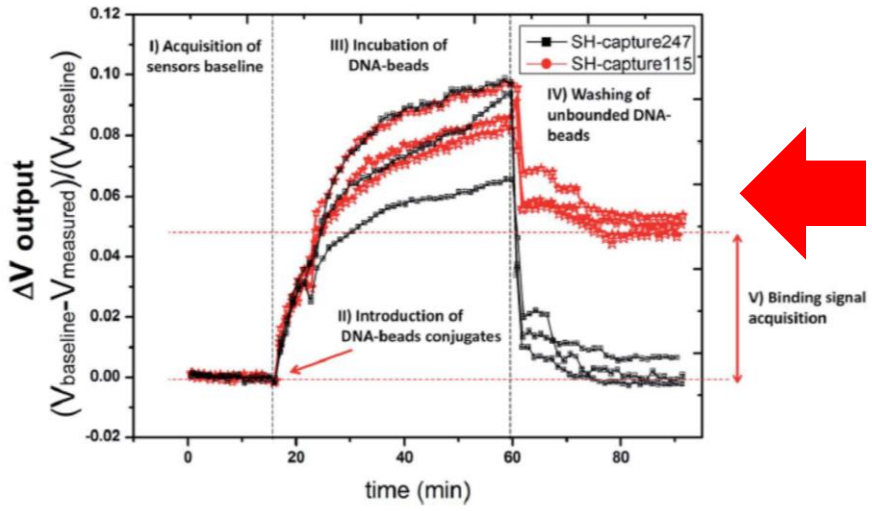
5-PCR (thermal), 6-re-labelling

7-Probe spotting on MR chip

(microspotter)

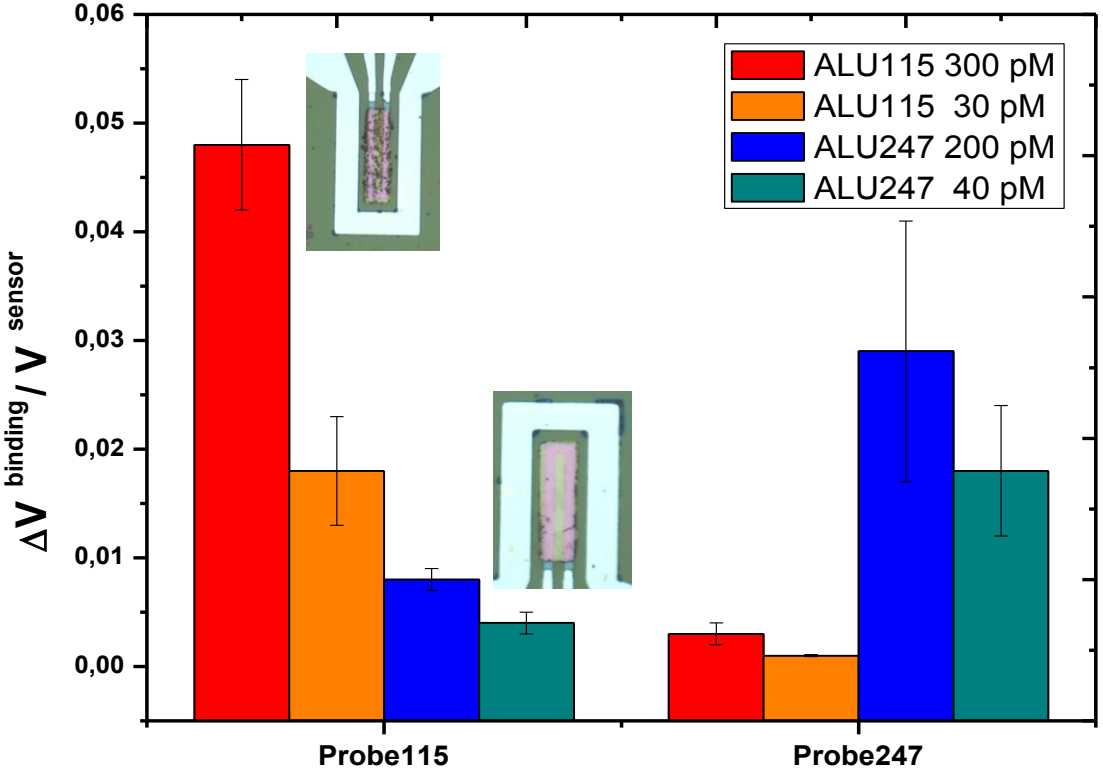
8-Sample analysis on MR platform

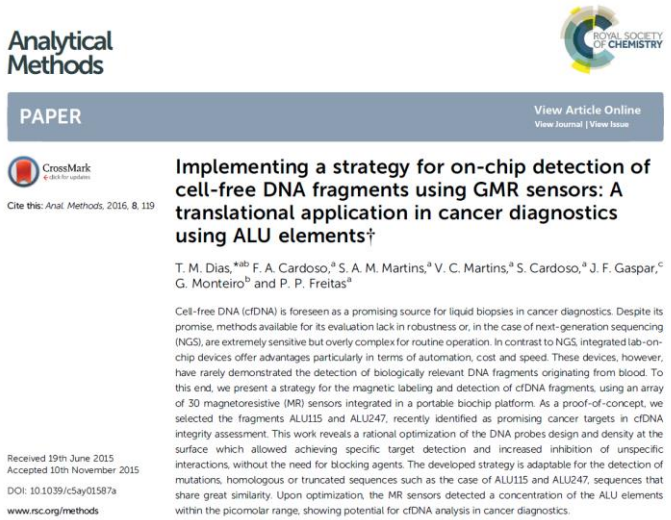
(pressure sealed single channel µ-fluidic chamber)



On-chip detection

On-chip detection and distinction between the two target fragments simultaneously (ALU115 and ALU247) with no cross-reactivities: spiked labelled DNA targets on PB





Analytical Methods

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Cite this: *Anal. Methods*, 2016, 8, 119

Implementing a strategy for on-chip detection of cell-free DNA fragments using GMR sensors: A translational application in cancer diagnostics using ALU elements†

T. M. Dias,*[ab] F. A. Cardoso,[a] S. A. M. Martins,[a] V. C. Martins,[a] S. Cardoso,[a] J. F. Gaspar,[c] G. Monteiro[b] and P. P. Freitas[a]

Cell-free DNA (cfDNA) is foreseen as a promising source for liquid biopsies in cancer diagnostics. Despite its promise, methods available for its evaluation lack in robustness or, in the case of next-generation sequencing (NGS), are extremely sensitive but overly complex for routine operation. In contrast to NGS, integrated lab-on-chip devices offer advantages particularly in terms of automation, cost and speed. These devices, however, have rarely demonstrated the detection of biologically relevant DNA fragments originating from blood. To this end, we present a strategy for the magnetic labeling and detection of cfDNA fragments, using an array of 30 magnetoresistive (MR) sensors integrated in a portable biochip platform. As a proof-of-concept, we selected the fragments ALU115 and ALU247, recently identified as promising cancer targets in cfDNA integrity assessment. This work reveals a rational optimization of the DNA probes design and density at the surface which allowed achieving specific target detection and increased inhibition of unspecific interactions, without the need for blocking agents. The developed strategy is adaptable for the detection of mutations, homologous or truncated sequences such as the case of ALU115 and ALU247, sequences that share great similarity. Upon optimization, the MR sensors detected a concentration of the ALU elements within the picomolar range, showing potential for cfDNA analysis in cancer diagnostics.

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Accepted 10th November 2015

DOI: 10.1039/c5ay01587a

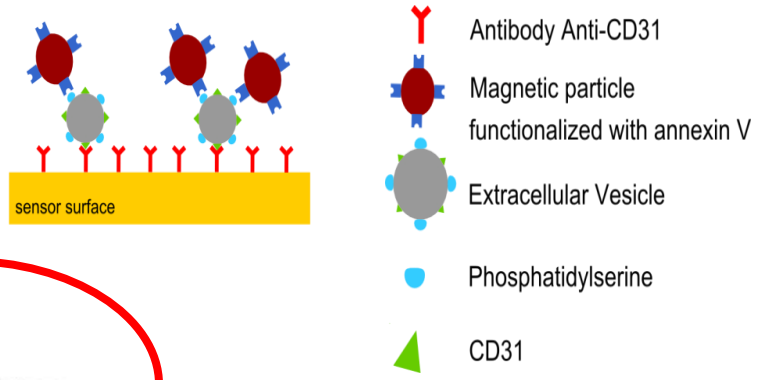
www.rsc.org/methods

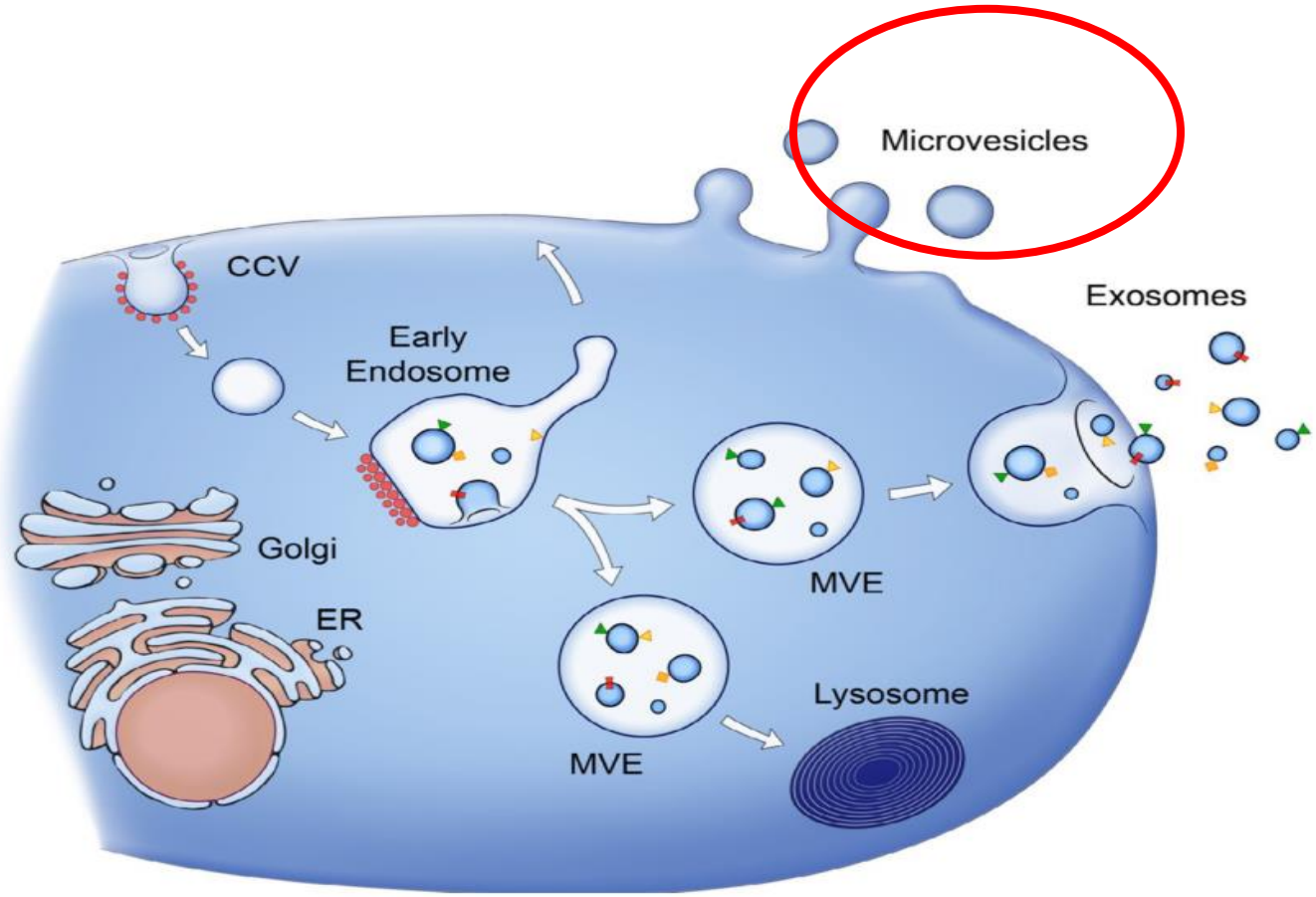
*Data obtained from the average of different sensors for each of the measurements (min = 8 sensors; max = 12 sensors)

New experiments in collaboration with Andresen Cancer Institute, Austin

2-Cell-derived microvesicles (MVs) in blood/serum (novel diagnostic biomarkers)

Which extracellular vesicles we're looking for?

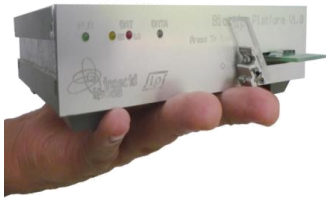


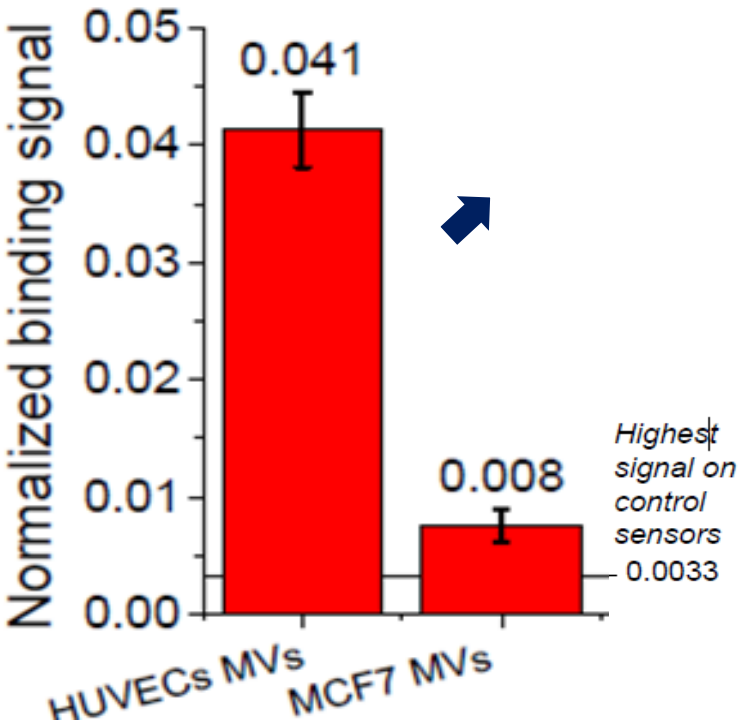


Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 200:373–83. doi: 10.1083/jcb.201211138

Microvesicle detection using a multiplexed biochip platform

Selective detection and quantification of MVs derived from endothelial cells (HUVECs)-extracellular media





Detection of HUVEC MVs on the MR biochip. Normalized binding signal on the specific sensors for the HUVEC MVs and the MCF7 MVs. The error bars represents the standard deviation of at least four independent sensors.

A clinical relevant concentration ($1x10^8$ MVs/ml) was detected by using this technology!

HUVECs MVs were detected specifically with a signal five times higher than the signal from the MVs derived from the epithelial cells MCF7;

Bios.Bioelectr, 2017