CENIMAT

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# Biosensor Research Activity at CENIMAT/i3N

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## Introduction

**Biosensors** are defined as analytical devices incorporating a biological material intimately associated with or integrated within a physicochemical transducer or transducing microsystem. These devices have been applied to a wide variety of analytical problems in several scientific fields, such as **medicine**, **biomedical research**, **drug discovery** and **point-of-care**. Here, we present different approaches for biosensor production and applications, currently under development at **CENIMAT/I3N**: (i) paper-based colorimetric sensors (Lab-on-Paper); (ii) ion sensitive field-effect transistors; (iii) PDMS-based microfluidics (Lab-on-a-Chip) and (iv) digital microfluidics.

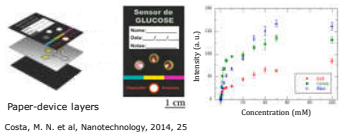
## Lab-on-Paper

Lab-on-paper is a novel technology to produce **inexpensive**, **easy to fabricate** and **easy to use** paper-based devices for **point-of-care** diagnostic, by an eco-friendly **wax-printing technology**.

### Production steps


### Applications

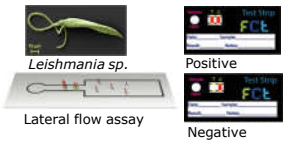
**Enzyme detection** Glucose measurement



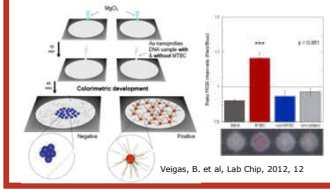

Paper-device layers

Costa, M. N. et al, Nanotechnology, 2014, 25

**Immunoassay** Leishmania diagnostic

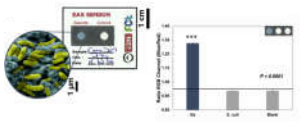



**DNA identification** Tuberculosis diagnostic




Veigas, B. et al, Lab Chip, 2012, 12

**Electrochromic detection** Bacteria detection



$$WO_3(white) + xe^- + xM^+ \leftrightarrow M_xWO_3\ (blue)$$

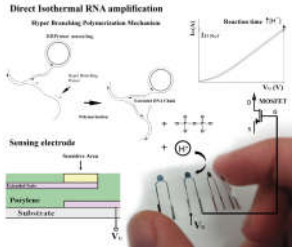
Marques, A. C. et al, Sci Rep, 2015, 5

## Ion sensitive FET biosensor

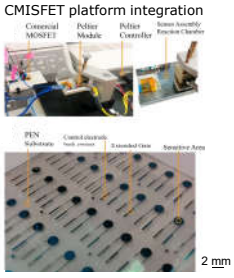
**Ion sensitive** charge modulated ISFET based sensor was integrated with real-time DNA/RNA **isothermal rolling Circle Amplification** (RCA) techniques for cancer biomarker genes, allowing for the real-time quantification of template and direct gene expression-profiling platform.

### Application

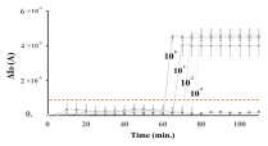
Charge modulated ISFET sensing



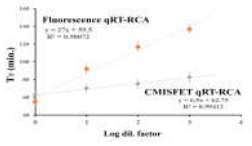

CMISFET platform integration




Real-time quantitative hyper branched RCA for BCR-ABL gene fusion.




qRT-RCA with 10-fold dilutions of initial BCR-ABL RNA template showing CMISFET RT-RCA amplification curves.




Relationship between copy number of initial DNA sample and threshold time (CMISFET and standard fluorescence)

Veigas, B. et al, Biosens. Bioelectron, 2017

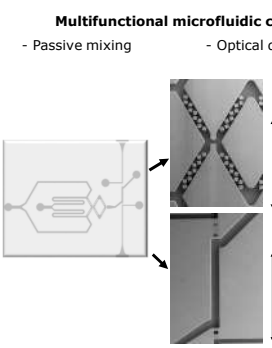
## Lab-on-a-Chip

Lab-on-a-chip (LOC) is a device at millimeter/centimeter scale that integrates **one or more laboratory functions** on a **single chip** to allow a high-throughput **screening**. Usually they are combined with microfluidics to operate, allowing: **low** fluid **volumes** consumption; **faster analysis** and **response** times; process **control**; **compactness**; massive **parallelization**; **low** fabrication **costs.**

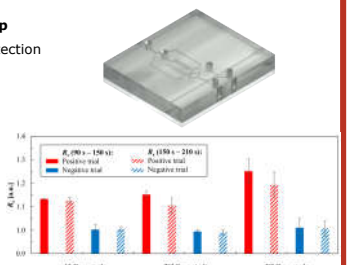
### Applications

**Multifunctional microfluidic chip**

- Passive mixing
- Optical detection




Schematic of a multifunctional PDMS chip. It comprises a passive mixer of stepped diamond shaped obstacles and rectangular contraction between rhombi, and a chamber for optical detection.




As an application towards the screening of Chronic Myeloid Leukemia, 3 case study pairs were evaluated: **1st** hybridized Au-nanoprobes with/without salt (proof-of-concept); **2nd** hybridized Au-nanoprobes mixed with synthetic oligo (complementary/non-complementary) and salt; **3rd** hybridized Au-nanoprobes mixed with RNA extracted from culture cells (K562, positive for BCR-ABL1 / THP1, negative control) and salt, as an approach to a clinical trial.

Alves, P. U. *et al*, submitted for publication (LSA,2017)

## Digital Microfluidics

Digital Microfluidics (DMF) is a versatile technique for **individual droplet control** (micro- to picolitre scale), over an electrode array. This technique relies greatly on **electrowetting-on-dielectric** (EWOD), a phenomenon in which there is a **change in the contact angle** of a liquid over a dielectric surface, **as a response to an electric field**.

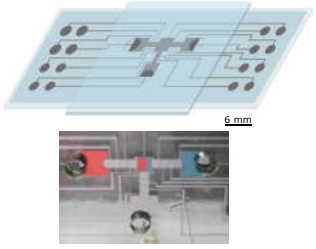
### Applications

DMF has an enormous potential for chemical and biological reactions: chemical synthesis, cell monitoring, proteomics, immunoassays, etc.

**@CENIMAT**: DMF chips for nucleic acid amplification, envisioning the detection of proto-oncogenes, for **cancer point-of-care diagnostics**.

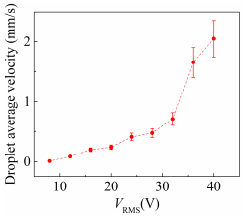
DMF chips developed @ CENIMAT for point-of-care diagnostics.

Total **reaction volume under 2µL**.




**Droplet** average **speed**: **2.1 ± 0.3 mm/s**

@ 40 $V_{RMS}$, 5kHz.




## Conclusions

Biosensors are an emerging technology that is not fully explored yet. There is still room for improvement regarding the detection principles, fabrication, designs and output signal-to-noise ratios. Despite that, they have already proven to be valuable assets for the industry with particular interest for applications in the health sector. Biosensors have already attracted the interest of many companies and they may soon detain a considerable share of our society consumption.

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