UNIVERSITÀ DI PARMA

DIPARTIMENTO DI SCIENZE CHIMICHE, DELLA VITA E DELLA SOSTENIBILITA' AMBIENTALE

Società Chimica Italiana
Gruppo Sensori

Società Chimica Italiana
Divisione di Chimica Analitica
Gruppo Bioanalitica

# *Workshop "From molecules to devices"*

## 6 Dicembre 2019

*Centro Congressi Santa Elisabetta*
*Campus Universitario, Parma*

Working Group "Dalle molecole ai dispositivi"
Laboratorio Comp-Hub del Dipartimento di eccellenza

*PROGRAMMA*

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|---|---|
| 9:00 | *Registrazione dei partecipanti* |
| 9:15 | *Saluti e introduzione ai lavori*<br>*G. Dieci, Direttore del Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale (SCVSA)*<br><br>*M. Careri, Coordinatore del Working Group "From Molecules to Devices" nel progetto del Dipartimento di eccellenza*<br><br>*M. Mirasoli, Coordinatore del Gruppo di Bioanalitica, Divisione di Chimica Analitica, Società Chimica Italiana* |

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|---|---|
| 9:30 - 13:00 | NANOTECHNOLOGIES FOR SENSING AND DEVICES<br>CHAIR: W. KNOLL |
| 9:30 - 10:10 | **Plenary lecture**<br>NATURE-INSPIRED LUMINESCENT BIOSENSORS AND RELATED MATERIALS<br>A. Roda |
| 10:10 - 10:40 | **Key-note lecture**<br>DNA-BASED NANODEVICES FOR DIAGNOSTIC APPLICATIONS<br>F. Ricci |
| 10:40 - 11:00 | *Coffee Break* |
| 11:00 - 11:20 | MOLECULAR DEVICES FOR PCR-FREE DNA DETECTION<br>S. Petralia, L.E. Sciuto, G. Forte, M. Zimbone, M.L. Di Pietro, G. Valenti, L. Prodi, S. Conoci |
| 11:20 - 11:40 | DOPAMINE POLYMER APPLICATION FOR THE DEVELOPMENT OF (BIO)ANALYTICAL DEVICES<br>P. Palladino, S. Scarano, M. Minunni |
| 11:40 - 12:00 | A PORTABLE INTERNET OF THINGS (IOT) BIOSENSOR FOR POINT-OF-CARE APPLICATIONS<br>I. De Munari, V. Bianchi, M. Giannetto, M. Careri |
| 12:00 - 12:30 | **Key-note lecture**<br>BIOSENSING IN DROPLET MICROFLUIDIC DEVICES WITH PERSPECTIVES IN DIGITAL BIOASSAYS<br>G. Spoto |
| 12:30 - 13:00 | **Tavola Rotonda**<br>"FROM MOLECULES TO SENSING DEVICES" NEL DIPARTIMENTO DI ECCELLENZA<br>Moderatore: A. Roda<br>Intervengono: R. Corradini, E. Dalcanale, M. Giannetto |

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| 13:00 - 13:45 | *Lunch Break* |

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| 13:45 - 16:15 | FROM SMELL SENSORS TO OPTICAL SENSING DEVICES<br>CHAIR: A. RODA |
| 13:45 - 14:25 | **Plenary lecture**<br>SENSING SMELLS<br>W. Knoll |
| 14:25 - 14:45 | TAILORING OLIGOPEPTIDES AND hpDNA FOR THE REALIZATION OF GAS SENSING ARRAYS<br>D. Compagnone |
| 14:45 - 15:05 | A SMARTPHONE-BASED DEVICE FOR PIGMENTS DETECTION BY IMAGE ANALYSIS<br>R. Calvini, G. Foca, A. Ulrici |
| 15:05 - 15:25 | MOLECULES, ORGANIC, BIO-ORGANIC SYSTEMS AND FUNCTIONALIZATIONS FOR SMART DEVICES: FROM SENSING TO BIO-ELECTRONICS TO NEUROMORPHIC SYSTEMS<br>S. Iannotta, S. Battistoni, T. Berzina, V. Erokhin, P. D'Angelo, C. Peruzzi, G. Tarabella, D. Vurro, V. Ricci |
| 15:25 - 15:40 | *Coffee Break* |
| 15:40 - 16:10 | **Key-note lecture**<br>LONG PERIOD GRATINGS AND MICROBUBBLE RESONATORS AS EXTREMELY SENSITIVE LABEL FREE OPTICAL PLATFORMS FOR BIOSENSING<br>F. Baldini |
| 16:10 - 16:30 | CHEAP, SMART AND RELIABLE TECHNOLOGY FOR OPTICAL BIOSENSORS AND DIAGNOSTIC TOOLS<br>M. Sozzi, A.M. Cucinotta, A. Candiani, S. Selleri |
| 16:30 - 16:50 | PORTABLE CHEMILUMINESCENCE-BASED BIOSENSORS: NEW LATERAL FLOW IMMUNOASSAY DESIGN AND NANOMATERIALS FOR ULTRASENSITIVE DETECTION<br>M. Zangheri, I. Trozzi, L. Anfossi, F. Di Nardo, C. Baggiani, M. Mirasoli, A. Roda |
| 16:50 - 17:00 | *Concluding remarks* |

# SILICA NANOPARTICLES AS LUMINESCENT PLATFORMS FOR IMAGING AND SENSING APPLICATIONS

L. Prodi

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Silica nanoparticles are versatile platforms with many intrinsic features, including a low toxicity. Proper design and derivatization yield particularly stable, very bright nanosystems displaying multiple functions [1], which can be used for either otpical and photoacoustic imaging [2] and for photoluminescence (PL) [3] and electrochemi-luminescence (ECL) sensing [4]. In addition, silica nanoparticles can also be used for as platforms for photo-dynamic and photo-thermal therapies.[2] For these reasons, silica nanoparticles already offer unique opportunities, and further improvement and optimization can substantially expand their possible applications in fields of high impact, such as medical diagnostics and therapy, environmental and food analysis, and security. In this context, we have developed a direct micelle assisted strategy based on the use of Pluronic F127 as high molecular weight surfactants. The one-pot synthesis yields PEGylated silica nanoparticles endowed with very high monodispersity, colloidal stability and core-shell structure. These nanoparticles were recently reported with the acronym PluS NPs (Pluronic Silica NanoParticles). These NPs had a silica core of about 10 nm and an overall hydrodynamic diameter of about 25 nm. Interestingly, PluS NPs can be tailored for optimization of processes such as directional energy transfer, which provide those systems with extremely valuable functions: high light-harvesting capability, signal-to-noise maximization, multiplex output, and signal amplification. *In-vivo* experiment proved the absence of toxic effects.
We will focus our presentation to the use of these systems for imaging and sensing applications, such as the possibility to monitor the presence of illicit drugs.[4]

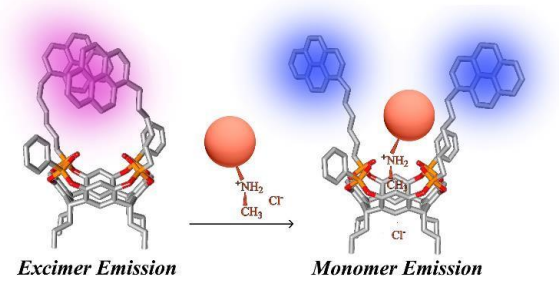


**Figure 1:** Sensing mechanism for the detection of ecstasy [4].

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# DNA-BASED NANODEVICES FOR DIAGNOSTIC APPLICATIONS

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Nature has invented a number of tricks and strategies by which the behaviour of proteins and other biomolecular machines can be finely controlled. These highly optimized and evolved mechanisms allow to control biological pathways with different chemical and environmental stimuli and are at the basis of the high specificity and selectivity of biomolecular machines.
Motivated by the above arguments we have characterized and recreated in-vitro several mechanisms to control the response of DNA-based nanodevices for diagnostic and drugdelivery applications. Using these mechanisms we can finely control the activity of DNA-based nanodevices with different chemical and environmental stimuli including pH, antibodies, enzymes, small molecules and electronic inputs.
I will present an overview of the most representative and recent examples developed in our lab in the above research directions focusing on examples of DNA-based nanodevices for diagnostic applications.

# MOLECULAR DEVICES FOR PCR-FREE DNA DETECTION

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The development of portable devices able to carried out genetic analysis, the so-called *Genetic "Point-of-Care"* (PoC), represents one of the most intriguing fields in the biomedical research matching the vision of future home-made molecular diagnosis by microchips integrated into smart mobile devices (i.e smartphones or smart watches). Since nowadays the sequence of thousands of genomes is known [1], genetic POCs are particularly relevant opening the possibility to massively use the molecular analysis with significant progresses in many fields, not only in medicine, but also in forensic science, food and anthropology.
The current gold standard methods for genetic analysis are based on the PCR (Polymerase Chain reaction), allowing the amplification of a specific genetic sequence through thermal cycling and the catalytic action of the polymerase enzyme. However, this biotechnology includes several analytical steps and needs complex instrumentation. This limits its use in centralized laboratories. To overcome these limitations, new analytical methods for nucleic acids (NAs) (DNA, RNA) analysis are mandatory to design genetic PoC to be used in decentralized environments (outside the laboratory) near the patient [2].
In this context the new frontier of research is the development of new biochemical strategies to allow NAs detection without any amplification step (*PCR-free methods*). This will have a tremendous impact on the rapidity of the analysis as well as the reduction of the final system complexity and energy consumption.
In this contribution two *PCR-free* approaches are presented and discussed. The first approach is based on *Intercalative Label and Cooperative Hybridization* (Fig 1 a). This method uses a chemical detection strategy based on a cooperative hybridization of a whole genome with two complementary capture probes (single strand DNA ) immobilized on electrode surface. The genome is therefore immobilized on the electrode surface and its direct detection is achieved by electrochemical intercalative probe [Os(2,20-bipyridine)(dipyrido[3,2-a:2′,3′-c] phenazine)])$Cl_2$ via the monitoring of square wave signal. This method has been proved to reaches a LoD (Limit of Detection) of HBV (Hepatitis virus) comparable to the standard qRT-PCR method of 20 copies/reaction [3]. Further studies using electro-chemical luminescent (ECL) labels (such us $[Ru(phen)_2(DPPZ)_2]PF_6$) reaches LoD of 10 cps/reaction for HBV analytical sample.
The second approach is *Label free Cooperative Hybridization* and it has the ambition to avoid any use of detection label (Fig 1 b). In this case the detection is achieved by the interaction of the whole genome immobilized on a surface with the surface itself. LoD up to 2 copies/reaction has been recently demonstrated on Si NWs (nanowires) surface through quantum confinement luminescence quenching [4].
The PCR-free methods represents a fascinating field of research being very promising solutions for the future development of portable and easy-to-use genetic PoC devices.

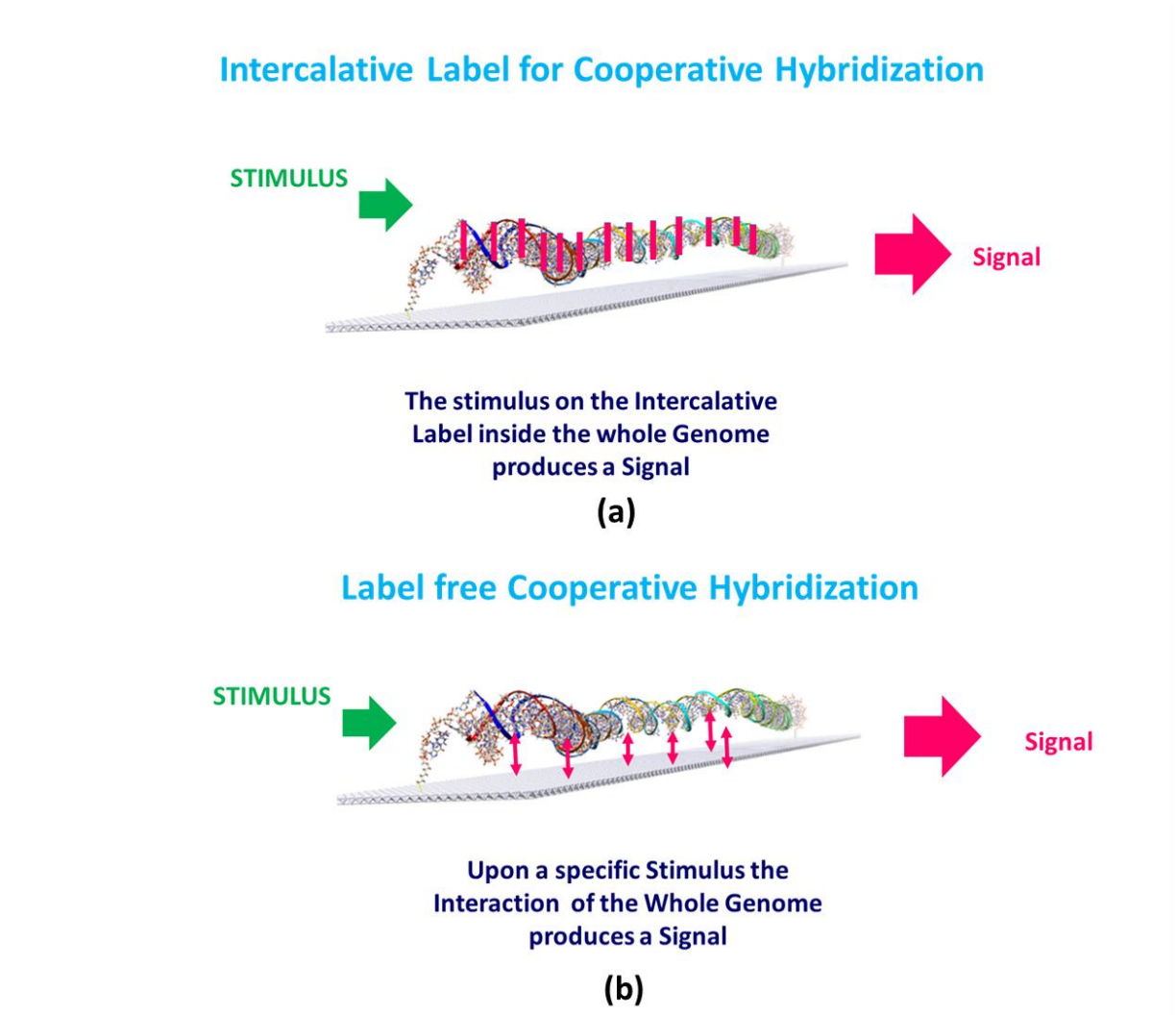


**Figure 1:** Scheme of PCR-free approaches: (a) Intercalative Label and Cooperative Hybridization; (b) Label Free Cooperative Hybridization.

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# DOPAMINE POLYMER APPLICATION FOR THE DEVELOPMENT OF (BIO)ANALYTICAL DEVICES

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The description of dopamine (DA) metabolism in the brain and peripheral areas allowed the explanation of age-related synthetic decline, the recognition of pathologies associated with concentration anomalies of DA and subsequent associated-drugs application in several medical conditions [1]. At the beginning of the 21st century the non-enzymatic oxidation od DA to *ortho*-quinone and the subsequent self-polymerization has generated several applications in medicine, (bio)analytical chemistry, and materials science [2-10]. In particular, a recent and intriguing outcome is represented by the electrochemical and chemical reaction pathway for polydopamine (PDA) formation in aqueous solutions. Notably, the last four years represent almost 80% of all the scientific production, underlining the enhanced interest arising from the versatile chemistry of this endogenous catecholamine and its complex polymerization mechanism. In particular, a promising field of PDA research is the surface coating for molecular sensing and affinity separation for pharmaceutical studies and clinical applications, following the peculiar physicochemical properties of PDA, and the molecular immobilization and imprinting capability of this biopolymer. Here we report a survey of this demanding area of bioanalytical research, focusing on the state-of-art of PDA applications for coating and imprinting, and offering a long-term vision for the capability of this polymer to be exploited to its full potential for the development (bio)analytical devices.

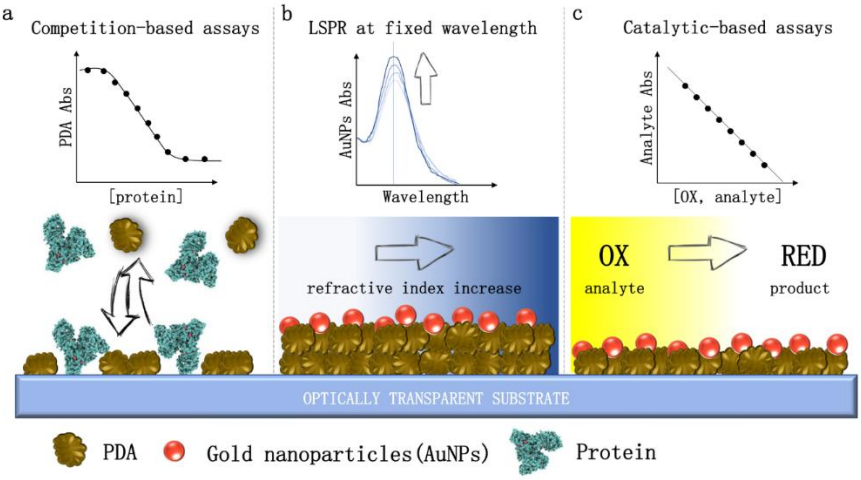


**Figure 1.** (a) Competition-based assay for quantification of total protein in biological fluids. (b) (LSPR)-based quantitative assay at fixed wavelength. (c) Catalytic-based assay for redox reactions. From reference [6].

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# A PORTABLE INTERNET OF THINGS (IOT) BIOSENSOR FOR POINT-OF-CARE APPLICATIONS

I. De Munari[1], V. Bianchi[1], A. Boni[1], M. Giannetto[2], M. Careri[2]

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In this work, a low-cost portable system suitable for analytical data acquisition from electrochemical biosensors is presented [1]. The system was designed for Point-of-Care applications to perform diagnostic tests and to provide rapid results without the use of costly and complex laboratory equipment to obtain accurate results. Even if innovative portable solutions have been recently proposed, usually they rely on PC or smartphones for data processing and they exhibit poor resolution, scarce portability and the need of proprietary software. The portable device exploits an ad-hoc designed analog front-end and a development board equipped with a system-on-chip integrating a microcontroller and a Wi-Fi network processor (Figure 1). Thanks to the flexibility of the Analog Front End (AFE), the proposed potentiostat can perform classical Differential Pulse Voltammetry (DPV) to measure the electrochemical cell current output, but it is also fully compatible with chronoamperometry and Square-Wave Voltammetry (SWV) measurements. In addition, the signal processing section can properly manage all three techniques.

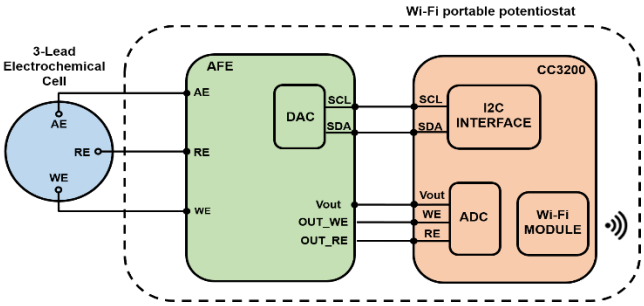
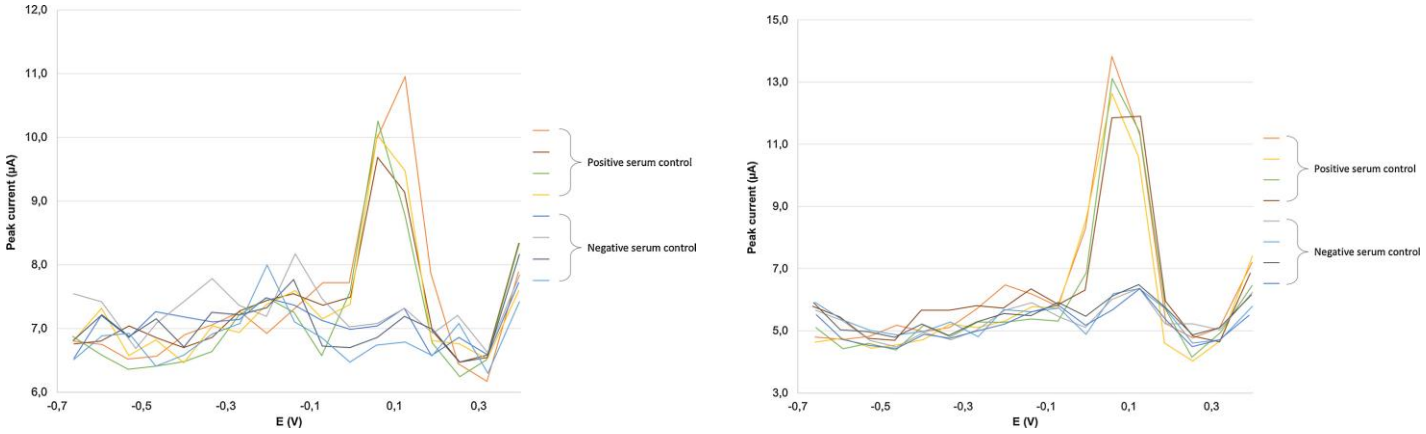



**Figure 1:** The portable device architecture

The wireless module is integrated into a Wi-Fi network architecture enabling the transmission of measurements directly to a cloud service for sharing the device outcomes with users (physicians, caregivers, etc.). In doing so, the system does not require customized software nor other devices involved in data acquisition. Furthermore, when any internet connection is lost, data are stored on board for subsequent transmission when a Wi-Fi connection is available.
To validate the effectiveness of the proposal data acquired with a conventional benchtop Autolab PGSTAT-204 electrochemical workstation were compared with the outcome of our developed device. To this end, ferri/ferrocyanide was selected as redox probe, obtaining the calibration curves for both platforms. The final outcomes proved to be feasible, accurate and repeatable. The designed device was applied in two cases of study: 1) the diagnosis of celiac disease and 2) the determination of ovarian cancer antigen human epididymis protein 4.
In the first case the target was a semi-quantitative analysis to discriminate between positive (sick) and negative (healthy) samples. Few measurement points were sufficient leading to a low computational complexity and, consequently, short processing time. The results show the

capability of the IoT-Wi-Fi device to discriminate effectively between positive and negative serum control [2], resulting suitable for diagnostic purpose (Figure 2).




(a) (b)

**Figure 2:** Signals recorded using the IoT-WiFi device for the determination of (a) anti-tTG human IgA; (b) anti-tTG human IgG.

In the case of the determination of ovarian cancer antigen [3], exploiting the high resolution of the AFE presented in [1], a total of 120 measurement points of the differential output current were collected, comparable with the number of points attainable with lab instruments.
Figure 3 attests quality of the signals recorded over the 350 fM-350 nM HE4 concentration range. The basedrift phenomenon has to be considered to correctly estimate the DPV peak current. For this purpose, for each measurement point, a baseline estimation algorithm was computed on-board.

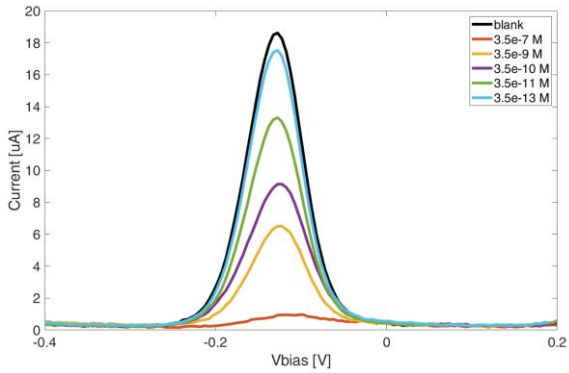



**Figure 3:** DPV scans recorded carrying out immunocompetition assays over the 350 fM-350 nM HE4 concentration range in human serum samples.

In conclusion, this work shows great promises for the application of the designed IoT portable electrochemical immunosensor for both qualitative and quantitative analysis, including perspectives for the implementation of the device in screening programs.

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# BIOSENSING IN DROPLET MICROFLUIDIC DEVICES WITH PERSPECTIVES IN DIGITAL BIOASSAYS

G. Spoto

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Droplet microfluidics has emerged as a key technology for biomolecular detection. Compared with the macroscale, the microfluidic environment offers essential advantages for biomolecular detection, such as reduced sample volumes required for the analysis, shorter analysis time, and potential for automation and integration. Such benefits are particularly desirable in nucleic acids amplification and detection.
The most renowned and today widely used nucleic acid amplification technology exploits the polymerase chain reaction (PCR). The method is simple, sensitive and cost-effective. However, it is prone to sample contamination and suffers from biases in the template to product ratios of the amplified target sequences. The method relies on the thermal cycling in vitro of the sample to reach a maximum of twofold amplification in each cycle.
The thermal cycling largely limits the application of PCR in resource-limited settings and for point-of-care (POC) analysis for which the full exploitation of advantages associated with the integration of nucleic acid amplification protocols in microfluidic-based devices is pursued. To overcome limitations arising from the need for thermal cycling, several alternative isothermal methods have been developed [1]. In fact, isothermal amplification does not require thermal cycling, thus greatly simplifying implementation in point-of-care diagnostics.
In this perspective, possibilities offered by the combined use of droplet microfluidics and the molecular beacon-assisted isothermal circular strand-displacement polymerization of nucleic acids is highlighted [2]. In particular, opportunities for DNA and microRNA amplification in nanoliter droplets and optical detection will be presented. High potentials offered by digital bioassays [3] are also highlighted and preliminary data from digital detection of nucleic acid sequences based on isothermal strand-displacement amplification.
Droplet microfluidics represents a convenient platform also for the detection of protein biomarkers. In this context, a droplet microfluidic-based approach that combines the gold nanoparticle-enhanced chemiluminescence with aptamer interaction to detect human lysozyme into droplets 20 nanoliters in volume is presented [4]. The described method allows identifying lysozyme with a 44.6 femtomolar limit of detection, using sample volume as low as 1 µL and detection time in the range of 10 min. We used luminol to generate the chemiluminescence and demonstrated that the compartmentalization of lysozyme in droplets also comprising gold nanoparticles provided enhanced luminescence. We functionalized the gold nanoparticles with a thiolated aptamer to achieve the required selectivity that allowed us to detect lysozyme in human serum.

**References**

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# SENSING SMELLS

W. Knoll

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For the sensing of light, e.g., in optical communication, we have extremely powerful devices with the ability to detect even single photons. Similarly, the monitoring of sound in acoustic communication is technically no problem: microphones are available with amazing performance parameters. Only for chemical communication, for smell or taste detection on a technical level, we have (nearly) nothing. Despite the fact that the monitoring of chemicals in chemotaxis, i.e., the molecules-guided search for food of many organisms or the exchange of chemical cues between species as a way to communicate with each other, is the oldest of our sensory repertoire, we have essentially no technical device that offers the sensitivity and the bandwidth needed to sense and to differentiate many different odors. Earlier attempts to fill this gap by “artificial noses” failed (with the only notable exception being the “alcohol breath analyser” used by police) mostly because of lack of sufficient sensitivity.
In order to develop and present during this talk concepts for smell sensors that could overcome these sensitivity limits we will very briefly refer first to the world of smells and give a brief introduction into how mammalians and insects smell.
Using a biomimetic approach, i.e., using functional elements (proteins) from nature and combining them with electronic devices for hybrid transducers, we describe novel schemes and read-out concepts for smell sensors.

# TAILORING OLIGOPEPTIDES AND HPDNA FOR THE REALISATION OF GAS SENSING ARRAYS

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Gas sensor arrays, often reported as electronic noses, have proved to be very useful tools for the analysis of foods and flavors. These tools can be applied to quality control (including shelflife, food freshness, volatile fingerprints) in a wide range of food as coffee, tomato, meat, milk, fruits [1]. The use of gas sensor arrays in the food industry represents an opportunity considering their sensitivity, high correlation with conventional sensory evaluation, short analysis times, low cost, non-invasive measurement. Quartz crystal microbalances (QCMs) represent one of the simplest configurations in gas sensing. These sensors have the potential for sensitive and selective target gas detection; their surface can be easily modified with organic compounds taking advantage of the measurement run at room temperature [1]. The use of short peptide sequences and hpDNA loops, as binding elements in the gaseous phase, is particularly interesting as they can be easily synthesized and designed using virtual screening to bind molecular targets of interest. The majority of the work was carried out using an instrument developed by Tor Vergata Sensors Group (University Tor Vergata, Rome) that consisted of 12 quartz crystal microbalances (QMCs) in the same measuring chamber. We exploit the characteristics of ZnO nanoparticles to act as a carrier for six different pentapeptides (IHRIC, KSDSC, LAWHC, LGFDC, TGKFC and WHVSC), and Au nanoparticles to act as a carrier for the HpDNA loops that were extended with a double helix stem of four bases (GAAG to 5' end and CTTC to 3' end). A virtual screening approach was used to evaluate the affinity of peptides [2] and hpDNA [3] against different classes of molecules (Figure 1), and, then, selected peptides and hpDNA were immobilized on piezoelectric transducers.

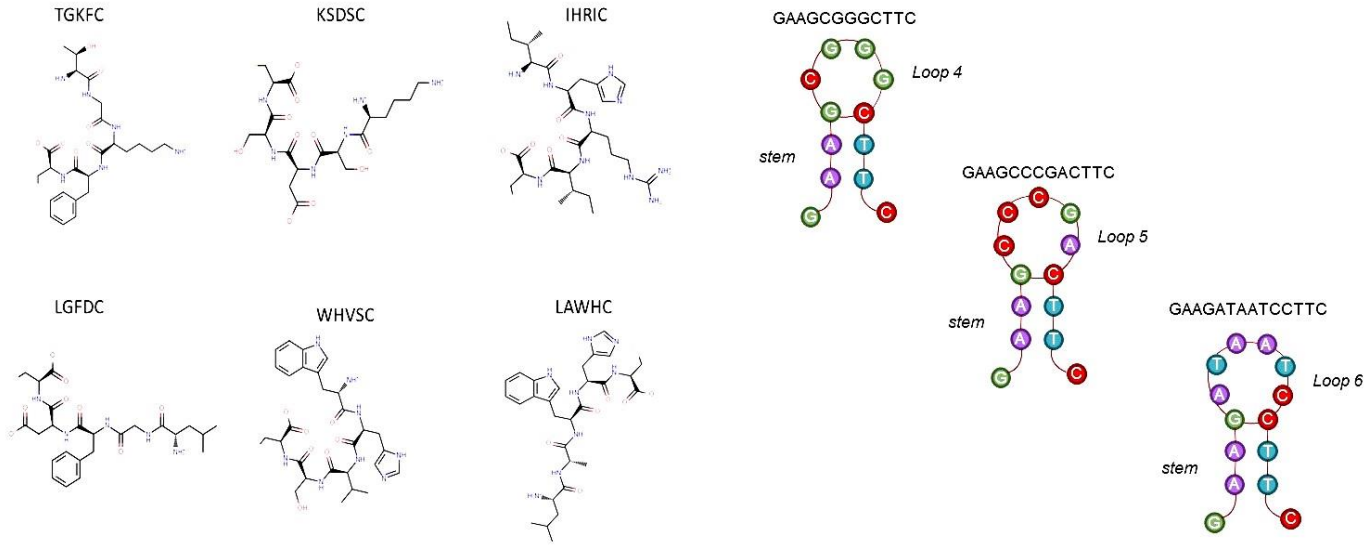


**Figure1:** Structure of penta-peptides and HpDNA with different loop size

The realized gas sensing arrays were used to discriminate different aroma compositions in food or plants.
It was demonstrated that ZnONPs-peptides and AuNPs-hpDNA are able to work with samples having high content of water (fruit juices, carrots). The results showed the ability of these gas sensor array both to discriminate among samples kept at different temperatures and to monitor the volatile compounds change during time, with good stability of the signal (no drift in 4-6 months ) and repeatability (interday RSD below 20% ) [4 - 6].
The peptide based array was used also to evaluate volatiles in commercial pasta of different prices and qualty. The results obtained with gas sensors array were comparable with the GC/MS analysis demonstrating that the array the array can be used for in situ quality control because of very little or no sample preparation and low cost [7].
Both peptides and hpDNA were also used for the development of an optoelectronic array based on SPRi technology. The developed array was able to discriminate aldehydes from alcohols with only 1-carbon atom difference [8]. Finally, the volatile composition of Cannabis sativa samples was also studied and a mixed array composed by hpDNA and peptides was successfully used to classify samples of different cultivars (having monoterpenes and sesquiterpenes in different amounts) demonstrating the potential utility also for samples rich in terpenes. Also in this case the results was compared with GC/MS analysis [9].
In all the realized study discrimination classification was achieved via principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA) or hierarchical clustering analysis (HCA). In the case of Cannabis sativa, to achieve the psame performance of GC-MS it was necessary to analyze the data using an Artificial neural network (ANN).
In conclusion, short peptides and hpDNA appear as ideal candidates as binding elements in gas sensor arrays considering the possibility to “design” the array by molecular modelling, the low cost of instrumentation and sensors, little sample preparation, fast response time and robustness of the assay.

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# A SMARTPHONE-BASED DEVICE FOR PIGMENTS DETECTION BY IMAGE ANALYSIS

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One of the most important parameters used to determine the optimal grape harvest date is phenolic maturity [1, 2], which is related to the amount of anthocyanins in the grape skin. Currently, the determination of grape phenolic maturity requires expensive and time-consuming analytical procedures, involving various steps for the extraction of the analytical sample and its subsequent analysis by UV-Visible spectrophotometry and HPLC. In this context, we developed an alternative analytical method for the assessment of grape phenolic maturity directly in the vineyard, through chemometric elaboration of RGB images of grape berries acquired with a smartphone. To this purpose, grape samples from to two different varieties of Lambrusco (Ancellotta and Salamino) were collected at different harvest times, from veraison until complete ripening. RGB images of the grape samples were acquired with a device designed ad-hoc for this application, consisting in a smartphone coupled with a specific 3D -printed case containing a sample holder and a controlled illumination system. After image acquisition, the grape berries were also analysed by means of reference analytical methods for the determination of several physico-chemical parameters usually employed for the assessment of phenolic maturity, such as optical densities, colour index and the content of the main anthocyanins [3]. The RGB images of grape samples were firstly standardized using a colour reference, and then converted into unidimensional signals named colourgrams [4], which can be considered as a sort of fingerprints codifying the colour content of the images. The dataset of images was thus transformed in a matrix of signals, which were used to develop calibration models using Partial Least Squares (PLS) and interval PLS (iPLS) for the prediction of the analytical parameters related to grape phenolic ripening. The calibration models were then implemented into a dedicated app, which easily allows to acquire the images on-site, visualize immediately the corresponding parameters of interest, and share the predicted values and the relevant metadata by means of a web interface. The device allows to increase the frequency of measurements, to easily share and access to historical data, to speed up the harvest planning and to perform differentiated harvest of grapes with different maturation levels, thus offering the possibility to increase the quality of wine.

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# MOLECULES, ORGANIC, BIO-ORGANIC SYSTEMS AND FUNCTIONALIZATIONS FOR SMART DEVICES: FROM SENSING TO BIO-ELECTRONICS TO NEUROMORPHIC SYSTEMS

S. Iannotta[1], S. Battistoni[1], T. Berzina[1], V. Erokhin[1], P. D'Angelo[1], C. Peruzzi[1], G. Tarabella[2], D. Vurro[1], V. Ricci[1]

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Organic based Biosensing [1], [2], [3] and memristive devices [4], [5], [6], [7] are more and more paving the way to novel perspectives both in mimicking and interfacing natural systems while representing an ideally suitable platform for applications in bio-electronics and bio-medicine. Furthermore they represent a very promising playground for neuromorphic devices and systems. Our contribution to the field including applications to drug delivery studies and bioelectronics will be introduced and discussed together with the recent achievements in developing memristive devices based both on PANI/PEO and PEDOT::PSS polymers. Sensing has been developed in several directions for application to nanomedicine, drug delivery, and neuronal signaling. Fig 1. Shows shows the detection of drug induced stress by a chemoterapic molecules on cultivated cancer cells demonstrating the ideal suitability of our approach compared to standard more cumbersome methods.

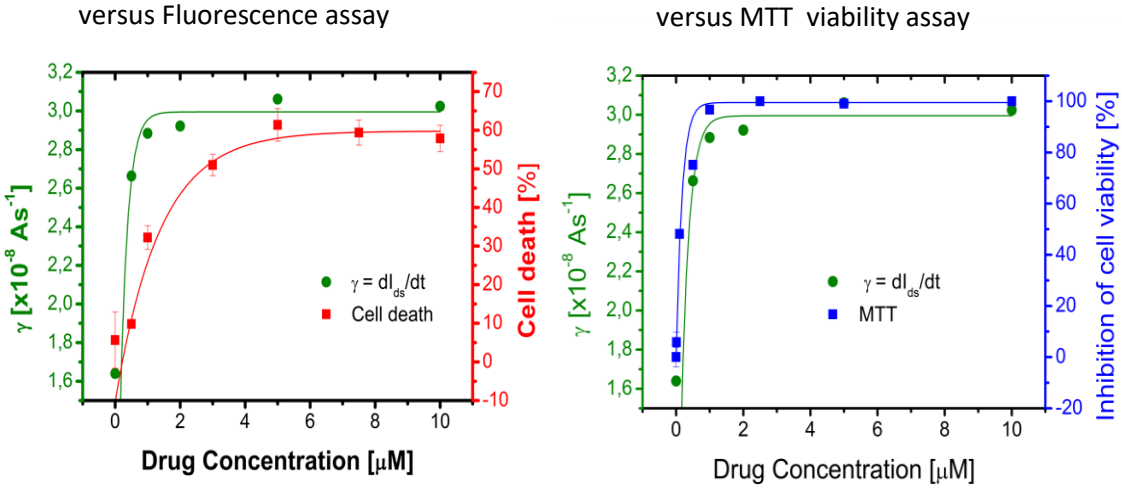


**Figure 1:** OECT monitoring drug -induced stress and death on A549 (human lung adenocarcinoma) and Human non-small-cell lung carcinoma (NSCLC) HCC cell line. OECT gives direct information on the effects of Doxorubicin, a typical drug used for the treatment also on the apoptotic besides necrosis [10].

The evolution from simple logic elements up to organic based Perceptron will be discussed envisaging the perspectives. The results and potential of the approach based on organic electrochemical devices will be discussed together with the great potential of these devices in the framework of other methods and technologies already established in the field. The novel approach based on interfacing memristive devices with biological cells and systems will be introduced together with the demonstration of a memristive organic-bio-hybrids that will be proposed and discussed as a potential for novel very promising applications. The interfacing of our memristive synaptic elements with neuronal cells with the experiment shown in fig. 2, has

demonstrated the feasibility of producing devices working neuromorphically together with natural brain elements, activating the neuronal response as it occurs in the natural systems.

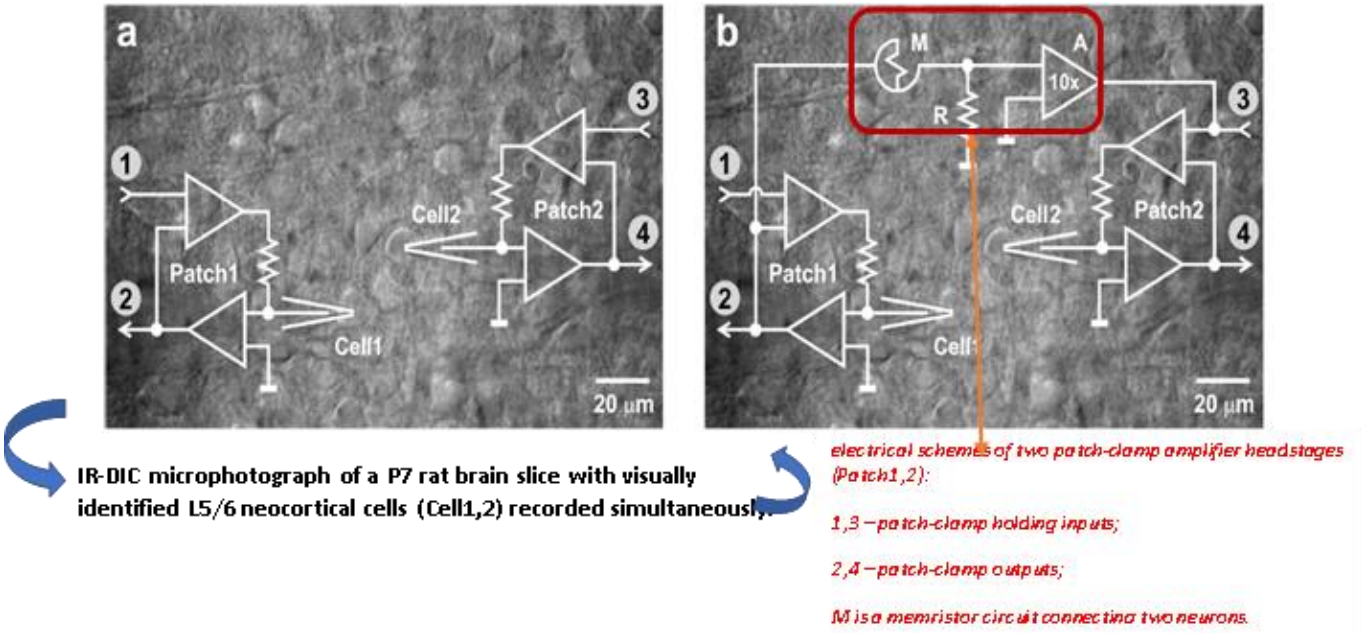


**Figure 2 :** A memristor device has been coupled to two non communicating neuronal celle of a cotex of a rat demonstrating via patch clam experiments the ability of our organic memristor device to function exactly as a natural Synapsys [8].

The results demonstrate for the first time, down to the finer details in the bioelectronic signaling and temporal response of the two memristively interconnected neurons, the same expected behavior for the natural synapsis interconnected neurons.

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# LONG PERIOD GRATINGS AND MICROBUBBLE RESONATORS AS EXTREMELY SENSITIVE LABEL-FREE OPTICAL PLATFORMS FOR BIOSENSING

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Measurements of refractive index in biological fluids are being used since many years for the quantitative measurements of analytes, by means of the use of chemical/biochemical recognition layers deposited on suitable substrates. Optics plays an important role in this area thanks to the use of different approaches/platforms: surface plasmon resonance; interferometric configurations; resonating structures.

Long period gratings [1, 2] and optical ring resonators [3] have been recently proposed for chemical and biochemical sensing, being characterized by high sensitivity to external refractive index.

LPGs are characterized by a periodic modulation (i.e. the grating period Λ) of the core of a single-mode optical fiber and they are highly sensitive to the changes of the refractive index (RI) of the medium surrounding the fiber due to the coupling occurring between the fundamental core mode and different cladding modes. Due to the intrinsic nature of LPGs, the fiber transmission spectrum is characterized by a series of attenuation bands centered at specific wavelengths (i.e. the resonance wavelengths $\lambda_{res}$) that verify the phase-matching coupling condition. Any interaction occurring along the sensing region modifies the transmission spectrum and this can be evaluated in real-time by recording the $\lambda_{res}$ shift. Figure 1 shows a schematic illustration of an LPG -based biosensor. The literature up to now details three different approaches for enhancing the performance of an LPG in terms of RI sensitivity: by increasing the cladding mode order (thus by decreasing Λ) from low-order cladding modes to highorder ones (standard LPGs) [5], by coupling to a special dual-resonance LPG in which the high-order cladding mode exhibits a turn-around point (TAP) in its phase-matching curve (TAP LPGs) [6] and by depositing on the fiber a nm-thick overlay characterized by a RI higher than the fiber cladding RI (coated LPGs or LPGs in modal transition) [4].

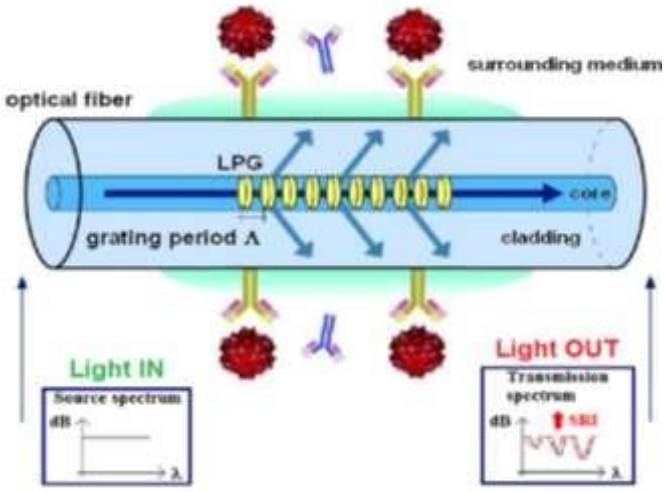


**Figure 1:** Schematic illustration of the light coupling in an optical fiber LPG and of the effect of surrounding RI (SRI) changes on the transmission spectrum (from ref 4].

An important aspect, which should not be underestimated, is the fact that in the LPGbased biosensors the analyte under investigation interacts with a recognition layer immobilized on the fiber. Therefore, the important parameter to be considered in order to correctly analyze the LPG performance, which should be taken into account and which sometimes is neglected, is the comparison between the penetration depth of the evanescent field and the thickness of the region where the chemical/biochemical interaction takes place (and not simply the total extent of the penetration depth of the evanescent field).In addition to these interactions, LPGs are also able to measure temperature and strain changes and mechanical interaction. Therefore, in order to achieve high accuracy and precision in evaluating the RI changes, it is essential to implement a reliable and effective mechanical and thermal stabilization in the measuring apparatus [7].

Among the optical ring resonators, those achieved by considering the transversal cross-section of a glass capillary as resonating structure [3], has the enormous advantage of eliminating any problems associated with the integration of the microfluidics and the optical resonator. In particular microbubble resonators (Figure 2), intended as spherical bulges realized in hollow silica microcapillaries, are very promising since they present the advantage of incorporating in the same device the exclusive properties of resonators, with embedded microfluidics ensured by the microcapillary itself are able to integrate the microfluidics.

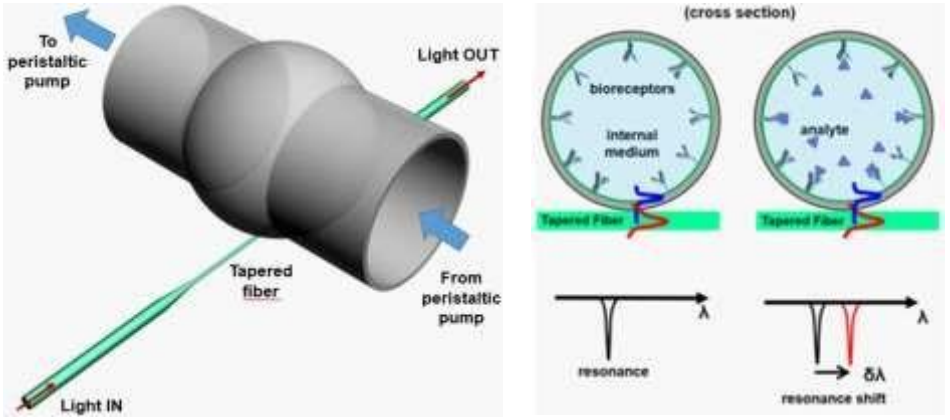


**Figure 2:** Left: schematic illustration of the microbubble resonator; the tapered fibre is used to couple the light to the optical ring resonator. Right: cross-section of the glass capillary, with the biosensing layer implemented in correspondence of the microbubble.

In this case it is essential implementation of the sensing layer in the internal wall of the glass capillary only in the correspondence of the microbubble; this feature can be achieved by means of a selective photo-activated immobilization [8].

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# CHEAP, SMART AND RELIABLE TECHNOLOGY FOR OPTICAL BIOSENSORS AND DIAGNOSTICS TOOLS

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Many research groups all over the world have been focusing efforts to define smart, reliable and low cost approaches and procedures for bioanalysis [1]. Among them, point-of-care analyses and colorimetric diagnostic assays can be effectively obtained by means of paper-based colorimetric test strips [2] where the variation of the analyte concentration generates a variation in the strip colour. This variation is usually checked, by naked eye, comparing the colour of the test strips with a colorimetric reference scale and it is affected by humans that may naturally perceive same colours differently due to physiological reasons and environmental lighting conditions. To avoid this subjectivity in the analysis, in the last few years, digital scanners and smartphones have been proposed. In particular, two main approaches have been adopted to solve these problems [3]. In first one, the strip and the reference colours system are acquired under the same environment condition and digitally compared [4]. This approach allows to work in uncontrolled environment condition but is target-dependent, since requires a different reference system for each chemical parameter to be analysed. In second approach, the target values are acquired in a totally controlled environment by using external devices or physical supports that must be designed for the specific smartphone model [5].
The new developed approach is target-independent and allows colorimetric analysis in uncontrolled environmental condition, by combining an application and a universal colorimetric reference system. The application acquires the image containing the dipstick and the target-independent colorimetric reference. Then, through the colorimetric equalization algorithm, it equalizes the colour distortions introduced by the environment condition and by the smartphone image processing, and estimate the chemical value of the analyte [6]. Figure 1 shows and example of the effectiveness of the algorithm, reporting the values of the maximum colour difference ΔE94 before and after the equalizing algorithm considering a set of sample test colours. Notice that this parameter evaluates the differences between colours taking into account human perception and values of ΔE94 < 3 are not perceptible by human eyes. In the test reported in Figure 1 the main value obtained after equalization is ΔE94 = 2.17.

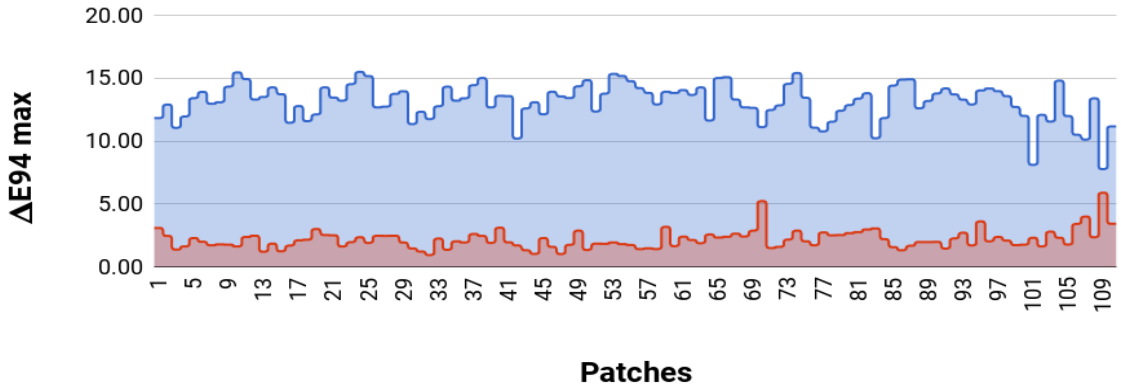


**Figure 1:** Values of the measured maximum colour difference ΔE94 before (blue) and after (red) the equalizing algorithm considering a set of sample test colours.

As an example, this approach has been applied to evaluate the concentration of nitrates in water. The equalized colour of unknown samples was compared with the mean calibration curve using again the colour difference ΔE94 and the obtained results are reported in the following table.

| Real concentration [mg/L] | Measured concentration [mg/L] |
|---|---|
| 150 | 125 |
| 375 | 350 |
| 25 | 25 |
| 100 | 100 |
| 75 | 75 |

**Table 1:** Comparison between the known (left) and measured (right) values of nitrate concentrations in water.

The proposed system delivers good results which well match the real values, also acquiring the test strips under various environmental illumination conditions. It thus represents a new and reliable approach for bio-sensing applications.
In conclusion, the approach allows target-independent colorimetric analysis in uncontrolled environmental condition without any external devices applied to the considered smartphone, and can be applied in all fields where a fast and low cost analysis is based on colorimetric dipstick tests, like environmental and clinical applications or food analysis.

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# PORTABLE CHEMILUMINESCENCE-BASED BIOSENSORS: NEW LATERAL FLOW IMMUNOASSAY DESIGN AND NANOMATERIALS FOR ULTRASENSITIVE DETECTION

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Lateral Flow Immunoassay (LFIA) is a technology currently widely applied in resource-poor or non-laboratory environments (point-of-care, POC) that is based on prefabricated strips of a carrier material containing dry reagents that are activated by applying the fluid sample. The conventional LFIA are available mostly for qualitative analyses, but the use of enzymes as tracers, coupled with chemiluminescence (CL) detection, provides highly sensitive quantitative assays [1]. Biosensors based on CL-LFIA are very promising analytical tools for rapid on-site detection of analytes in complex matrices.

Here, we report about the latest advances in CL-LFIA based technologies and their applications in different fields. Thanks to the intrinsic simplicity of CL detection principle, several portable and sensitive CL detectors can be designed to obtain a fully-integrated system. In addition, to reach the goal of portability, ready-to-use disposable cartridges containing all the reagents necessary to complete the analysis must be developed.

Nowadays, the improved imaging technology of the Back side Illuminated Complementary Metal Oxide Semiconductor (BI-CMOS) sensors used in smartphone cameras make them suitable for fast and accurate POC diagnosis based on CL-LFIA [2]. These biosensors will be useful in all situations where a decentralized and fast detection is required, taking advantage of the location (GPS) and wireless long distance data transfer ability. We applied this technology in different fields, from the detection of clinical biomarkers to the evaluation of mycotoxins food contamination. In particular, different formats for the LFIA cartridges were designed for combining compactness and ease of use. Accessories able to transform the smartphone into a CL detector were developed using a desktop 3D printer.

Since CL system employs labile enzyme that makes it hard to routinely use them for on-site applications, it is proposed to stabilize the HRP-labeled reagent testing different kind of preservatives in order to enhance the long-term stability of the enzyme and also to simplify the assay procedure.

The more actual approach is based on Thermochemiluminescent (TCL) probe which allows to realize reagent less device thus facilitating the development of simple instrumentation particularly suitable for developing country rural area. Indeed, TCL is a chemical luminescence phenomenon in which photons are emitted upon thermally-induced fragmentation of a suitable molecule, with production of a moiety in its singlet electronically excited state [3].

The proposed biosensors are user-friendly, extremely small and thanks to the integration with smartphone, they can be used in a wide range of situations: at home, in first aid departments, in containment departments for infectious diseases, in ambulances, in military centers, on cruise ships or in areas where an accident has occurred.

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