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Salt and Pepper for Point-of-Care Diagnostics

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Abstract

Currently available Point-Of-Care-Testing (POCT) devices usually suffer from complex test formats and transduction technologies unfavorable for automation. Among optical sensor technologies, the Reflectometric Interference Spectroscopy (RIfS) is particularly well suited for generating miniaturized, robust and disposable sensors. RIfS systems are not only suitable for diagnostic applications, but are also a good choice for other areas of life-science analytics including biotechnology, food monitoring and safety engineering. Users take advantage of the direct test format by avoiding laborious sample pre-treatment as well as addition of costly reagents, both being common disadvantages of competing test systems.

Keywords: Reflectometric interference spectroscopy, biointeraction analysis, optical transduction, point-of-care testing

1. Salt & Pepper technology

A miniaturized POCT device based on a direct test format has the potential to outrange even established methods on the market in regard to measurement speed and cost efficiency. Hereby, the handling of such a miniaturized device, which is used close to the patient, in medical practices or in the patient's home, must be possible without having special scientific knowledge (Push-the-button strategy). The outcoming quantitative and diagnostically relevant results should be directly available for the doctor in attendance. These results can be used for a continuous monitoring or for a decision about a new therapeutic strategy.

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Within the currently running project, the idea of creating a viable device out of an already constructed breadboard is realized. The goal of the project is a fully integrated prototype, being able to measure already developed clinically relevant diagnostic assays, both cost-effective and reproducible. Furthermore, all elements, which allow for automated execution and evaluation of measurements like an external fluidics, are kept really small and simple. In this way, a miniaturized device could be built, which is very user friendly and cheap in the components, and therefore can be used as prototype for a possible series production. But even this approach is already able to produce scientifically relevant results in regard to surveys carried out in a clinical environment. The aim is to close the gap between scientific research and development of a successfully economic utilization.

The successful development of the Salt & Pepper prototype was possible, because of using well-established technologies. The combination of the label-free technique RIfS together with a direct test format offers herein great advantages. Simple and easy to use detectors can be combined with cheap and simple disposable cartridges. The result is an optical transducer including a biological sensitive layer in combination with a detection system consisting of spectral sensitive photo diodes[1] and computation logic on one miniaturized chip assembly.

1.1. Reflectometric Interference Spectroscopy (RIfS)

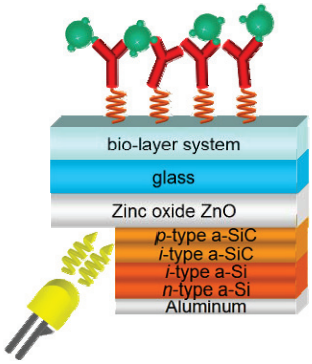

Fig. 1: piin-photodiodes on multi layered transducer. On the surface the biological receptors are located.

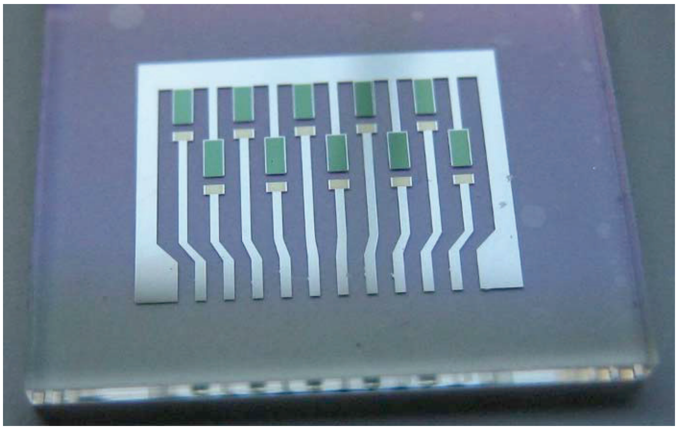

Fig. 2: Picture of electrode structure on glass transducer. The rectangles in green represent the photodiodes.

The interaction of analytes with the surface was monitored using RIfS. Principles and experimental set-up of this technique for monitoring binding events at interfaces were discussed in detail before[2, 3]. Changes in optical thickness of a thin silica-layer of about 330 nm thickness upon analyte binding are detected by interference of white light, reflected at the interfaces of a multilayer system, using a diode array spectrometer. Binding curves were recorded as apparent optical thickness versus time.

1.2. Characterization of biological interactions with the integrated chip

The measurement principle of the Pepper & Salt technology is comparable to measurements on a standard RIfS system. Changes in optical thickness, caused by the biological interaction of receptors on the transducer surface with ligands located in the solution flushing it, are detected by observing changes in the interference of light reflected from the bottom side. The signal is recorded with piin-semiconductor diodes vaporized on the non bio-functionalized side of the substrate (Fig. 1 and Fig. 2).

Purpose of the integrated chip is point-of-care diagnostics, i.e. the detection of clinical relevant analytes like markers for cardiovascular diseases or inflammations. Successful measurements for different markers were shown both in buffer solution (Fig. 3) and human serum (Fig. 4).

For a clinical usability the integrated device has to pass the rapid prototyping process after having successfully tested the laboratory pattern (Fig. 5). Therefore a miniaturized fluidics including a disposable cartridge system, micro pumps and a device control system were developed and combined in a common housing. Each component being in contact with samples and thus are contaminated, are disposable i.e. the combination of the cartridge system and the detection unit (Fig. 6). Because of the developed design all other parts apart from the aforementioned cartridge system, are barred from a possible contamination.

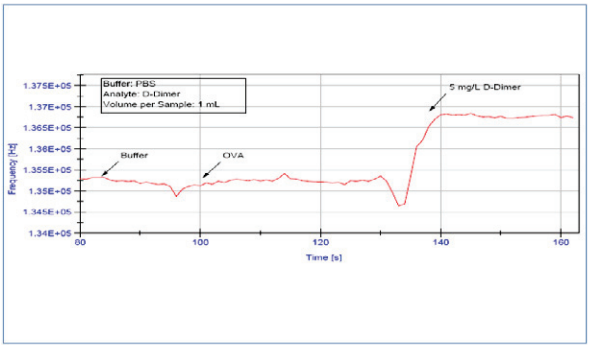

Fig. 3: Detection of 5 mg/l D-dimer in PBS buffer solution with the integrated chip assembly.

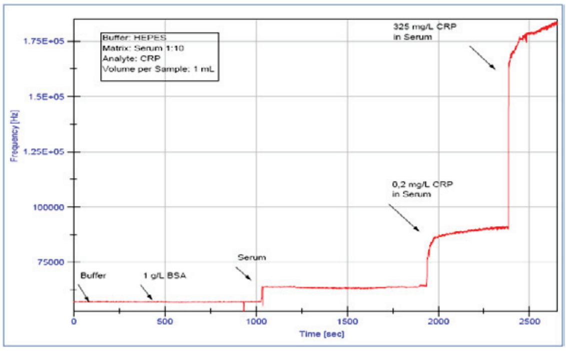

Fig. 4: Detection of different CRP (C-reactive protein) concentrations in human serum with the integrated chip assembly.

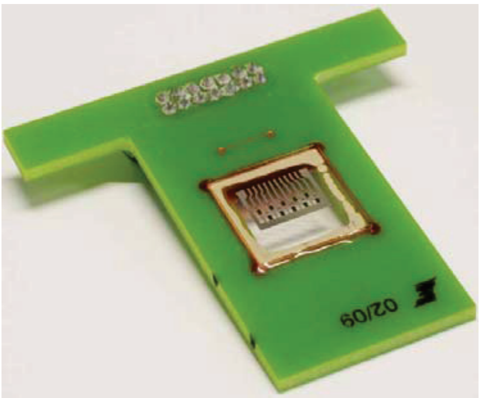

Fig. 5: Integrated detection unit combining an optical transducer with spectral sensitive photo diodes.

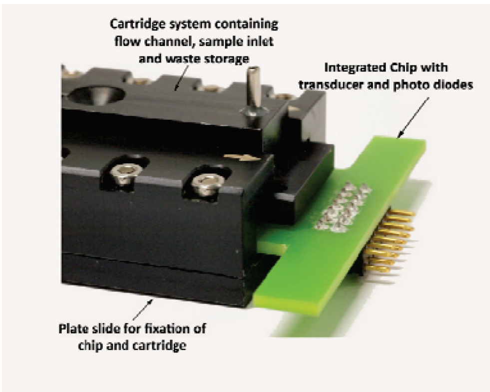

Fig. 6: Integrated detection unit combining an optical transducer with spectral sensitive photo diodes.

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