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Wireless Integrated Biosensors for Point-of-Care Diagnostic Applications

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Abstract

Recent advances in integrated biosensors, wireless communication and power harvesting techniques are enticing researchers into spawning a new breed of point-of-care(POC) diagnostic devices that have attracted significant interest from industry. Among these, it is the ones equipped with wireless capabilities that drew our attention in this review paper. Indeed, wireless POC devices offer a great advantage, that of the possibilityof exerting continuous monitoring of biologically relevant parameters, metabolites andother bio-molecules, relevant to the management of various morbid diseases such asdiabetes, brain cancer, ischemia, and Alzheimer's. In this review paper, we examine three major categories of miniaturized integrated devices, namely; the implantable Wireless Bio-Sensors (WBSs), the wearable WBSs and the handheld WBSs. In practice, despite the aforesaid progress made in developing wireless platforms, early detection of health imbalances remains a grand challenge from both the technological and the medical points of view. This paper addresses such challenges and reports the state-of-the-art in thisinterdisciplinary field.

Keywords: CMOS; point-of-care (POC); wireless biosensors (WBS); integrated electrochemical sensors.

Introduction

The seminal technological breakthroughs achieved in the field of biomedical instrumentation and related technologies, remain powerless in the face on the morbidity of numerous diseases. yearly billions of dollars are spent on the management of such diseases. For example, the Food and Drug Administration (FDA) refrains on approving novel antibiotics for fear of breeding new strains of bacteria by fortifying the ones already in hand. As a counter-measure, the National Institute of Health(NIH) rang the Red-Alert as a warning for eventual infectious diseases outbreaks, given the fact that antibiotics are no longer an option [1]. Consequently, the NIH has encouraged research projects aiming at developing bioengineering means to manage such situations. For instance in this direction, no socomial infections were intensively addressed and the deployment of networks of wireless bacteria sensors in hospitals is being investigated and represents the quintessence of th e bioengineering field [2]. Early detection of health threatening factors is a powerful prevention tool that applies to the medical field in its entirety. Hence, the long term goal behind bioengineering is to develop novel micro- and nano-devices for biological and medical purposes in order to

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develop detection tools for an arbitrary disease and in an ideal case, the very same tools will convey treatment modalities. In this perspective, the long sought for Complementary Metal Oxide Semiconductor (CMOS)-based DNA sequencing chip, has been recently completed through integration of millions of Ion Selective Field Effect (ISFET) transistors with a micro fluidic device.

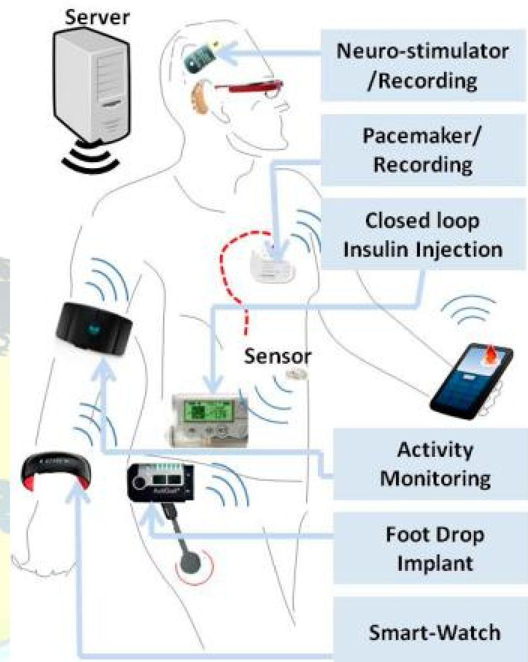
2. State-of-the Art in the Field of WBSs

In this section, we review the recent advances achieved in implantable and wearable biosensorsconceived for POC applications.

Implantable Biomedical Devices for POC Diagnostics

The field of implanted medical devices is turning into one of the most profitable businesses in USA,as these devices possess great advantages over their classical counterparts, since they offer betterimprovements to the quality of life of patients with chronic diseases, condemned to permanent anddaily use of bio-analytical and invasive tests. Hitherto, many implantable devices have been approvedby the FDA for a variety of applications ranging from monitoring of the glycemic index to thedetection of heart and brain electrical imbalances and palliation of hearing malfunctions [4–6]. In thebeginning, the main role of implanted devices was to replace a missing biological structure through useof prosthesis such as artificial hearts or support damaged anatomical structures like arteries through theuse of stents. Hence, as a natural to continuation in this field, miniaturized implantable biosensors for point-of-care diagnostics of diseases come about as the new generation of implantable medical devices that feature higher measurement sensitivities of physiological parameters

WBSs can be classified in three groups including, wearable, handheld and implantable devices suitable for the detection of various diseases.



Advances in Wearable WBSs Technologies

As described in the last section, modern medical devices have been designed and developed based on micro-sensors that exhibit wireless functionalities taken in the broadest sense, namely data transfer, energy transfer and leadless stimulation. The three aspects allow for real-time continuous monitoring of clinically relevant parameters, battery-less operating mode for long-term use and preservation of the integrity of the sensed/stimulated tissues, respectively. Despite the great capabilities of microelectronic technologies, the packaging of wearable WBS systems attached to skin surfaces remains a challenge given the fact that in such configurations, the WBS/skin

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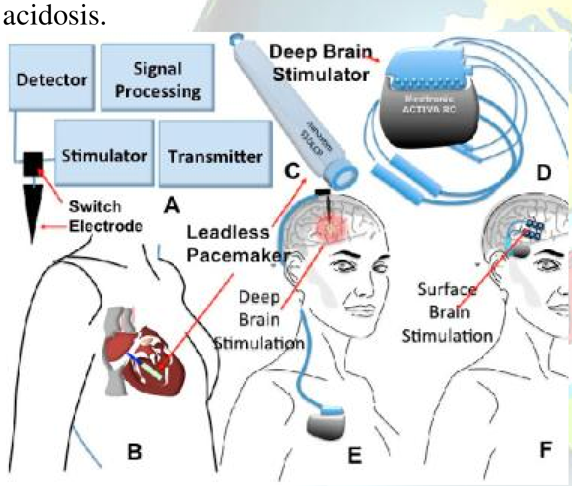
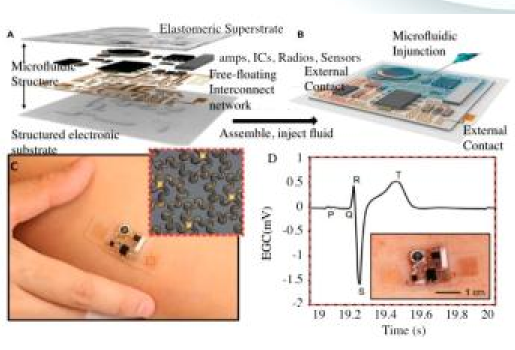
interface features cumbersome time-varying dynamics that are extremely hard to counteract. This technique resorts to an oxidized single-walled carbon nanotubes used as ox-SWNT functionalized with a conductive polymer called poly-amino anthracene or PAA used as a sensor. Awirelessly powered and passive Radio-Frequency Identification (RFID) tag was used to transmit pH data through simulated skin. The functionality of the proposed device was shown by changing the pH values. This device offers the advantage of making a viable means for early detection and potential prevention of bacteria colonization of surgical implants. Detection in this case is accomplished through monitoring of the bio film-induced acidosis.





Handheld Bio-Sensing Systems

Handheld biosensors are one of the most sought for analytical components to be added to the POCarsenal. Their field of applications ranges from classical glucometers to advanced devices for magneticimmunoassay tests [26,27]. A recently reported technique uses magnetic nanoparticles and immunoassayprotocols to measure concentrations of target molecules [28]. A disposable biosensor cartridge is insertedinto this hand-held analyzer for the measurement and the data are transmitted wirelessly to thebase-station. Another handheld system is the Stat-Strip Glucose Hospital Meter System that represents the first FDA-approved glucose meter that was for use in Intensive Care Units (ICUs) [29]. As these handled systems include a display screen and a Random-Access-Memory (RAM) and can be connectedto computers using wired data-links, wireless communication techniques do not play an essential role in most of these devices. In fact the wireless techniques are advantageous when information should be sent directly to the medical center to start decision making processes regarding an emergency or whencontinuous monitoring of the patients critical state is needed. To make a case for the usefulness ofwireless data transfer one should consider the genetic sequencing that is emerging as the ideal method fordisease diagnostics [30,31]. To date tremendous effort has been geared toward sequencing of DNA,DNA analysis and gene detection.

Toward Fully Integrated CMOS Based Biosensors

Standard micro fabrication technologies are the best candidate for the development of integrated POC systems. The foundries offer efficient mass-production platforms that lower the cost of microelectronics, making the price low enough to make electronic products affordable to the end-

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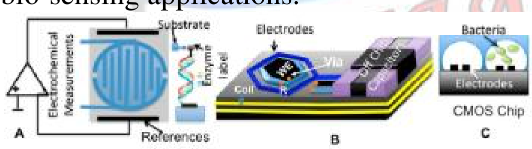
users. As to microchip scale of the integration, today's foundry processes have reached the threshold of 15 nm (minimum feature of Field-Effect-Transistors—FETs) and hence they allow for the making of highly dense systems featuring millions of active elements, which as a whole, form an integrated circuit (IC) used nowadays in a variety of industrial applications. In current uses, the advantage of standard microelectronic technologies, particularly CMOS, is the fact that they allow for creating monolithic integration of large numbers of micro-scale sensors/actuators along with their electronic circuitry. Such an approach allows the whole device to become capable of incarnating sensing techniques such as those based on optical, magnetic and electrochemical including impedometric, capacitive and ISFET techniques. Among these techniques, only electrochemical sensors offer the advantages of label-free detection, suitable for WBS purposes. For this reason, the focus of this section is placed on electrochemical biosensors as the best candidates for wireless integrated bio-sensing applications.



CMOS-Based Volta metric Sensors (Amperometry)

In volt metric techniques, by applying a DC voltage to an electrode, the relationship between
current and voltage becomes a function of the chemical/biological properties of species present in the sample. In this simple sensing method, a feedback circuit is used to apply a desired potential across the working electrode (WE) and the circuit interface used to measures the resulting current. The integration of the required circuitry for volt metric measurements on the very same chip that harbour the microelectrodes, significantly decreases the need for using current and voltage references and above all, the effect of parasitic capacitance that arises from excessive usage of interconnections
(electrodes and the measurement system) on the readout path, becomes drastically insignificant. Hence, volt metric or ampere metric circuitries can successfully and most efficiently be integrated in CMOS chips along with low-noise-amplifiers (LNAs) circuits to eliminate the non-idealises caused in principle by the flow of stray currents in sample solution. Table 1 shows different configurations that could be developed in a CMOS process and applied to various biological and chemical applications including DNA detection. Further, a chronocoulomb metric DNA detection is performed based on the
oxidation and reduction of labeling molecules attached to hybridized DNA target strands [48]. Someknown drawbacks to this method are; the background and offset signals originating from the presence ofthe electrochemical agents exacerbated by the double layer capacitance that forms between electrodes andelectrolytes. As a follow up to the work reported in [48], a novel DNA micro array developed in CMOS0.5 µm technology was reported to successfully overcome the aforesaid drawbacks.
In order to eradicate these non-idealities, the main innovation in this novel design is the use of a differential measuring scheme, a fast integration algorithm and an optimized value in the triggeringvoltage-steps [49].In another approach, a redox-cycling-based electrochemical array of 128 sensors is presentedin [50]. By applying oxidation and reduction potential on two interdigitated electrodes, the current flows through both electrodes. This current has two main components; the current initially

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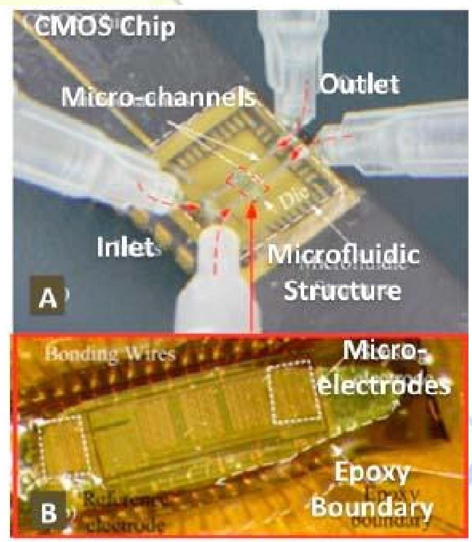
generated by the enzyme label and the current of the redox-cycling. Besides, and due to electrochemical artifacts, an offset current may also contribute to the total signal. Hence, instead of measuring the absolute value of currents, it is its first derivative with respect to time that yields useful information. The total measuring time is of the order of seconds to minutes. Using the same detection principle employed in [50], an improved chip of an array of DNA sensors was realized with as many analog to digital convertors as the number of sensors [51]. Here, again, in order to eliminate the offset current in the signals picked up by the proposed high dynamic range-sensing chip, it is the first derivative of the current with respect to the measuring time that is of interest. In the same work, a very simple integrated current-to-frequency converter is utilized. The accuracy of the conversion circuit is mainly determined by the process variations of the capacitors and also the comparator used in the analogue-to-digital converter (ADC).

CMOS-ISFET Sensors

Ion-Selective-FET (ISFET) can be described as a conventional Metal Oxide Semiconductor Field Effect Transistor (MOSFET) device with a floating gate. Here, a reference electrode inserted in an aqueous solution is electrically connected to the device through an ionic conductive electrolyte [65,66].A thin-membrane isolates the semiconductor active regions from electrolytes, so as any gradients in the concentration the ionic charge, modulates the ISFET threshold voltage (V_T). It is worth mentioning that the post-processing of fabricated standard chips can increase the cost of devices dramatically .Fortunately, ISFETs are fabricated in a standard CMOS process without necessitating any post-processing step, a fact that reduces their cost and allows the downsizing of these devices to more compacted form compared to their impedometric or conductive counterparts [67,68]. As depicted in the metal layers in a CMOS chip are employed to construct via between the CMOS passivation layers and the poly-silicon semiconductor. Furthermore, CMOS processes support the formation of epitaxial thin silicon nitride and/or silicon oxide for use as insulation layer(s) since these two materials are widely used for sensing applications due to their linear responses. In fact, ISFET could be employed for various applications such as DNA detection, extracellular imaging and cellular activities.



Conclusions

In this paper, the recent progress in the field of point of care diagnostic (POCD) devices were
described. The main challenge in developing wireless integrated biosensors is the development of
integrated sensors and circuits on the same chip. We also put forward the advanced CMOS techniques
used to develop electrochemical sensors. Among these, electrochemical impedometric, amperometric,voltometric

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and ISFET methods were comprehensively described, with further details of interfacecircuits and non-idealities, which can be compensated mostly using specific circuitries. The roadmap of point-of-care diagnostic technologies is the development of RF integrated sensors and actuatorsfunctionalized with recognition element for specific sensing purposes and CMOS will play a verycritical role to microchip scale integration technology in future development in this field.

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