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EXPERT OPINION

Wearable electrochemical sensors: innovative tools for the emerging mobile health ecosystem

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Introduction

With an estimated present global market of US$ 86.3 billion and expected annual increase around 7.9 % from now to 2020, sensors are nowadays one of the most active areas of research and technological developments [1] and a basic pillar of the emerging mobile health strategy that is expected to be revolutionizing healthcare in the near future. The biosensor and chemical sensor category is one of the most growing segment of this market, mainly due to increased use for medical purposes. Wearable electrochemical sensors conform a particularly flourishing category that benefits from the improvements in micro and nano fabrication of electrodes and instrumental components based on a range of new electrode materials (e.g. graphene). They are also expanding thanks to the widespread availability of advanced signal processing and management technologies on smartphones, tablets and similar portable devices. The aim of this contribution is to highlight the most outstanding recent progresses in the field of wearable electrochemical sensors for decentralized bioanalysis and show some examples of research trends that will shape the sector and expand applicability fields in the near future.

Wearable sensors in the context of the new mobile health ecosystem

Wearable electronic sensing devices and technologies, such as heart rate monitors, smart watches, tracking devices, smart glasses, and so on, are experiencing a period of rapid growth. Fitness dedicated devices are reported to be the most mature market, but there is a clear trend to combined devices including embedded sensors that track and analyze physical activity for self-control of training and physical status [2]. Wearable technologies will also influence future medical technology, affecting our health and fitness decisions, redefining the doctor-patient relationship and reducing healthcare cost, as part of the expanding mobile health concept that is currently under planning and deployment by health authorities and medical technology providers. There is an increasing focus on making healthcare more patient-centric so that patients can be empowered to manage their care improving lifestyles, enabling remote treatment of chronic conditions and informing healthcare providers to make better clinical decisions [3]. This is particularly important for monitoring elderly patients or chronic diseases in home settings, especially in remote locations or underdeveloped regions with limited or no access to conventional healthcare assistance.

Specific features of wearable electrochemical sensors

Electrochemical sensors represent an important subclass of chemical sensors that rely on the measurements of current, potential or charge at an electrode as analytical signals, which can be related to chemical parameters. Characteristics of electrochemical sensing devices include high sensitivity (down to the nanomolar levels) and selectivity, a wide linear range (typically 2-3 orders of magnitude), minimal space and power requirements, low-cost instrumentation, and a fast and cost effective response. So they are suitable for direct and reliable monitoring in harsh conditions, including a vast range of relevant applications in the fields of clinical, industrial,

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environmental and agricultural analysis [4]. The recent introduction of non-invasive wearable electrochemical sensors in bioanalysis are contributing to address key challenges, such as obtaining sensor response at trace and ultra-trace analyte concentrations, managing small biofluid sampling volumes, improve mechanical resiliency, enhance resistance to biofouling and better biocompatibility of the sensors [5, 6].

Minimally invasive sensors

Minimally invasive wearable sensors generally focus on measuring chemical properties in interstitial fluid (ISF), benefiting from accumulated experience on using this biological matrix for non-invasive detection of inherited metabolic diseases, organ failure, and drug efficacy. Extraction of the fluid is usually accomplished by the use of sub-cutaneous implanted micro-needle arrays that are connected with miniaturized, patch like electrochemical sensing wireless devices. Most of minimally invasive devices already on the market are devoted to glucose monitoring for patients affected by diabetes (mostly based on an enzyme-immobilized and amperometric detection), by applying proper correlation of glucose content in interstitial fluid and blood. The time lag between variations of the target analyte in blood and interstitial levels are also accounted [7]. Further improvements in this field are directed to fully implantable devices inserted at the adipose tissue levels, provided that a battery with sufficient durability and biocompatibility is available. In vivo electrochemical sensing of glucose and other analytes of interest is still hampered by problems like limited performance at analyte levels close to the detection limit, degradation and loss of electrode materials including modifying enzymes, interferences management and impact of biofilm formation [8].

Noninvasive sensors

Noninvasive sensors solve the perhaps most significant obstacle of minimally invasive devices which is biofouling (the accumulation and growth of undesired biomaterials on a surface) that rapidly and profoundly affects sensor sensitivity and durability by altering the sensor-body fluid interface. The best suited biofluids for applying noninvasive wearable sensors are sweat, saliva and tears. These biological fluids contain multiple physiologically relevant chemical constituents and can be readily obtained for non-invasive real-time monitoring of the analytes.

-Saliva. Saliva is a complex biofluid comprising numerous constituents permeating from blood via transcellular or paracellular paths, so it offers an excellent non-invasive alternative to blood analysis for monitoring emotional, hormonal, nutritional, and metabolic state of the human body. Salivary pH correlates with disposition towards developing dental caries, whereas lactate is related to physical stress and electrolyte concentrations may indicate amount of salt intake. An ideal salivary sensor must fit the complex anatomy of the mouth without disturbance for the wearer, and it must integrate wireless data transmission. Kim et al. [9] have developed a wearable non-invasive mouthguard amperometric biosensor for detecting lactate, which is the first example of a wearable electrochemical salivary sensor for continuous metabolite sensing. The sensor was fabricated on polyethylene terephthalate (PET) substrate and subsequently affixed to the outer side of the mouthguard for continuous salivary lactate detection. A dental tattoo has been tested for continuous wireless monitoring of respiration and certain types of bacteria by bio-functionalizing antimicrobial peptides on graphene-modified silk tattoo substrates [10], paving the way towards the development of a new class of metamaterial-inspired implantable biosensors.

-Tears. The concentration levels of glucose, lactate, or neurotransmitters in tears hold vital health significance. Ocular sensors are particularly defiant for sensor developers due to the very delicate nature of the target tissues. A number of earliest forms of ocular sensors have been fabricated on strip-based flexible substrates that are hardly biocompatible [6], so recent research is mainly focused on integration of sensing components in contact lenses. Probably one of the star projects towards employing tears as samples for physiological status measurements through non-invasive sensors is the smart lenses, under development at Google X labs [11]. The projected device consist on a tiny wireless chip and miniaturized glucose sensor embedded between two layers of soft contact lens material, for accurate glucose monitoring for diabetics, including LEDs to serve as early warning for the wearer. The concept is based on a previously reported amperometric enzymatic glucose sensor on a polymer substrate molded into contact lens shape for potential in situ monitoring in tear fluid [12].

-Sweat: Sweat analysis research is increasing in recent years due to its potential for non-invasive monitoring of markers of performance in sports, fitness and even military applications. The most straightforward application is the monitoring of fluid and electrolyte loss by athletes, but it can also serve for improved clinical management of certain pathologies where analytical parameters as pH, Cl^-, Na^+ or NH_4^+ can provide valuable diagnostic and therapeutic information [13]. A range of wearable sensors for sweat analysis is under development, mainly based on functionalized textiles and tattoos.

Commercial cotton yarns converted into electrical conductors by dyeing with a carbon nanotube ink, and then partially coated with a suitable polymeric membrane have been demonstrated as effective ion-selective electrodes for sensing pH, K^+ and NH_4^+ [14]. The cotton yarn potentiometric sensors were inserted in a band-aid for improved wearability. An amperometric sensor composed of a multiwall carbon nanotube (MWNT) functionalized nylon-6 material to quantify the amount of sodium ions in sweat in real-time has been designed and developed [15]. A recent review focused on wearable electronics and smart textiles clearly shows the potential of this field [16]. Recent advances in materials science producing flexible and stretchable fibers based on carbon nanotubes (CNTs) and graphene, and organic electronics are improving the characteristics of these type of sensors.

The tattoo concept for wearable electrochemical sensors oriented to sweat analysis has emerged as an alternative or complement to textiles. The main advantages of tattoos are that they can be fabricated at low cost with ample flexibility of design and constituents (based on the well-established screen printing technology), ensuring permanent and intimate contact with the skin. These features allow mass producing and storing of a range of sensors immediately available, easily implantable and removable by the user or by unspecialized personnel [13]. Tattoo sensors act as a secondary skin capable of maintain functionality under the continuous complex bending and stretching stress typical of human skin while the body performs various routine activities. A potentiometric tattoo sensor for pH measurement under physical training conditions has been reported [17], and the same group has reported similar potentiometric sensors for Na^+ [18] and NH_4^+ [19]. An epidermal lactate tattoo biosensor has been fabricated with carbon-nanotube/tetrathiafulvalene mediated lactate oxidase as the recognition layer, covered by a biocompatible chitosan overlayer. The biosensor operates at a very low potential of +0.05 V (vs pseudo Ag/AgCl reference electrode) for the chronoamperometric detection of lactate [20]. Very recently, a proof of concept for a tattoo based noninvasive glucose monitoring combining reverse iontophoretic extraction of interstitial glucose and an enzyme-based amperometric biosensor has been reported [21].

Future developments

The future perspectives of wearable chemical sensors are immense in diverse fields. New wearable sensors are being tested for important analytes as catecholamines and antioxidants in tears; cortisol and pathogens in saliva; or amino acids, calcium, and pathogens in sweat/ISF [6]. The fusion of several wearable chemical sensors should lead to non-invasive multi-analyte sensing. It is expected that the potential applications of wearable technologies will include the early diagnosis of diseases such as congestive heart failure, the prevention of chronic conditions such as diabetes, improved clinical management of neurodegenerative conditions such as Parkinson's disease, and the ability to promptly respond to emergency situations [22]. A complementary but very important issue to be improved is the availability of body worn energy harvesting and storage devices to power the sensing systems. Early efforts have resulted in the development of flexible batteries, piezoelectric nanogenerators, microsupercapacitors and endocochlear-potential-based biobatteries but significant improvements as tattoo based biofuel cells [13] are expected in the near future, coupled with low-power and energy/power-efficient technologies [23].

In summary, the accelerated progress in a vast range of sensing materials capable of sophisticated interaction with the human body, combined with autonomous power systems, miniaturized signal processors, and integration with radio frequency identification or Bluetooth devices, allow us to envisage a future where smart wearable machines will continuously sense our health status by monitoring a range of parameters as integral parts of our everyday outfits, even letting us share emotions, thoughts and sensations by interpreting chemical signals.

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