CellPress

Non-invasive wearable electrochemical sensors: a review

Amay J. Bandodkar and Joseph Wang

Department of NanoEngineering, University of California, San Diego La Jolla, CA 92093, USA

Wearable sensors have garnered considerable recent interest owing to their tremendous promise for a plethora of applications. Yet the absence of reliable non-invasive chemical sensors has greatly hindered progress in the area of on-body sensing. Electrochemical sensors offer considerable promise as wearable chemical sensors that are suitable for diverse applications owing to their high performance, inherent miniaturization, and low cost. A wide range of wearable electrochemical sensors and biosensors has been developed for real-time non-invasive monitoring of electrolytes and metabolites in sweat, tears, or saliva as indicators of a wearer's health status. With continued innovation and attention to key challenges, such non-invasive electrochemical sensors and biosensors are expected to open up new exciting avenues in the field of wearable wireless sensing devices and body-sensor networks, and thus find considerable use in a wide range of personal health-care monitoring applications, as well as in sport and military applications.

Why continuous non-invasive chemical sensing?

Chemical sensors and biosensors have been widely used as attractive alternatives to the bulky, expensive, and complex analytical instruments used in the health-care sector [1] (Box 1). Over decades, several of these devices have been developed for detecting vital analytes using optical, piezoelectric, and electrochemical transducers. Of these, electrochemical sensors have gained a dominating role in clinical diagnostics owing to their high performance, portability, simplicity, and low cost [2]. Substantial progress in electrochemical sensing has led to the development of commercial hand-held analyzers, such as the ACCU-CHEK (Roche Diagnostics, Inc.), iSTAT (Abbott, Inc.), or Lactate Scout (Sports Resource Group, Inc.), for detecting metabolites and electrolytes. However, most of these sensors rely on blood samples. The intrusive nature of these sensors thus poses a major hurdle to the patient and impedes the temporal information acquisition that is desired for diverse biomedical applications. This is especially true in the case of neonatal, elderly, and hemophobic patients, for whom blood sampling is challenging. Continuous analyte monitoring is of particular

Corresponding author: Wang, J. (josephwang@ucsd.edu).

0167-7799/

Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.tibtech.2014.04.005

Glossary

Amperometric sensors: devices that measure the current produced during the oxidation or reduction of an electroactive species at a constant applied potential. This current is proportional to the concentration of the electroactive product.
Biocompatibility: is a condition of being harmless to living tissue or a living system by not being toxic or injurious and not causing immunological rejection.
Biofouling: the accumulation and growth of undesired biomaterials on a surface.
Biofluid: a biological fluid. Biofluids can be excreted (such as urine or sweat), secreted (such as breast milk or bile), obtained with a needle (such as blood or cerebrospinal fluid), or develop as a result of a pathological process (such as blister or cyst fluid).
Biofuel cell: is a specific type of fuel cell that uses enzymes as a catalyst to oxidize its fuel and generate electricity.
Cariogenic potential: the ability of a food to cause tooth decay. It is evaluated by measuring plaque-pH during and for 30 minutes after consumption of the food product.
Conjuntiva: a thin membrane that covers the inner surface of the eyelid and the white part of the eyeball.
Electrochemical transducers: devices that convert chemical information into measureable electrical signal (such as current, voltage, charge, and impedance). Electrochemical transducers are utilized in fabricating electrochemical sensors in which the analyte concentration is proportional the recorded electrical signal.
GOx: glucose oxidase enzyme is an oxido-reductase that catalyses the oxidation of glucose to hydrogen peroxide and D-gluconic acid.
Hypotonic solution: a solution that has lower solute concentration as compared to its surrounding solution.
Keratoconjunctivitis sicca: is also known as dry eye syndrome. It is an eye disease caused by eye dryness due to either decreased tear production or increased tear film evaporation.
Non-invasive sensors: devices that do not require biofluids obtained by penetrating the body, as by incision or injection.
Optical transducers: devices that transform non-optical signal into an optical signal. They are widely used for developing optical chemical sensors. Such sensors convert chemical information into optical signal. The analyte concentration is proportional to the optical signal.
Paracellular transport: transfer of substances across an epithelium by passing through the intercellular space between the cells.
Polyethylene terephthalate (PET): a thermoplastic polymer resin. It is produced from ethylene glycol and dimethyl terephthalate or terephthalic acid.
Potentiometric sensors: devices that measure the electromotive force generated between two electrodes. The measured electromotive force has a direct dependence on the analyte concentration.
Plaque acidogenicity: the ability of a bacteria present in the dental plaque to form acids from fermentable sugars.
Reverse iontophoresis-based electrochemical sensing: is a technique that involves passing a mild current across two electrodes applied to the skin. This causes electro-osmotic flow of the metabolites from the subcutaneous layer to surface of the skin. The extracted ISF is then electrochemically analyzed and the analyte concentration is quantified.
Selectivity: is the ability of a sensor to identify the target chemical species present in a sample medium containing several other interfering chemicals.
Sensitivity: is the measure of the signal generated by a sensor upon exposure to unit analyte concentration.
Sialochemistry: a branch of chemistry that focuses on analysis of salivary composition.
Transcellular transport: transfer of substances through the cell, passing through both the apical membrane and basolateral membrane.

Box 1. Chemical Sensors/biosensors

The International Union of Pure and Applied Chemistry defines a chemical sensor as: ''a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal.'' A typical chemical sensor contains two basic functional units: a receptor and a physico-chemical transducer. If the receptor consists of a biological component (e.g., enzyme, antibody, DNA etc), the device is known as a biosensor (Figure I). The receptor transforms the analyte concentration into a chemical or physical output signal with a defined sensitivity. The main role of the receptor is to provide high selectivity towards the desired analyte in the presence of potentially interfering chemical species. The receptors thus help in obviating false-positive results. The transducer is another crucial component of the sensor that serves to convert the signal generated by the receptor–analyte interaction to a readable value. Biosensors can be distinguished based on their receptors, as either catalytic or affinity-based. Similarly, they can be classified according to the type of transducer used as electrochemical, optical, piezoelectric, and calorimetric sensors.

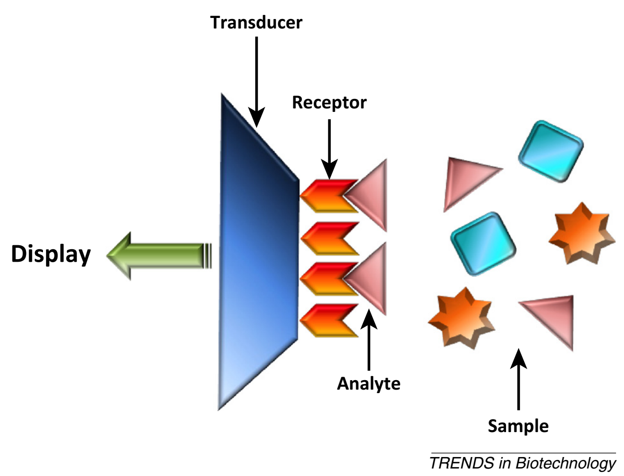

Figure I. Schematic showing important components of a typical sensor.

importance in different areas. For example, optimum diabetes management mandates regular glucose monitoring. Similarly, athletes require continuous assessment of their fitness level during training. Real-time detection of pathogens in biofluids (see Glossary) can alert the person about the plausible onset of disease. Monitoring drug efficacy is another scenario in which continuous measurements are of great importance. In the above-mentioned cases, invasive sensors have obvious limitations because continuous availability of the required sampling media (blood, urine, serum, and so on) is impractical.

Wearable sensors have received tremendous attention over the past decade [3–5]. These non-invasive devices offer considerable promise for continuous monitoring of a wearer's health, tracking exercise activity, and assessing soldier performance. By providing valuable real-time information, such wearable sensors allow individuals to change their lifestyle for maintaining optimal health status. The growing interest in wearable sensors reflects major shifts from centralized hospital-based patient care to home-based personal management, as the latter aims at lowering health-care costs.

Major endeavors towards on-body monitoring of wearer's health or fitness have resulted in the demonstration of a plethora of physical sensor devices [4,5]. Unlike wearable physical sensors for monitoring vital-signs, non-invasive chemical sensors and biosensors, which are based on the transduction of chemical information, are still in their infancy [3]. The limited availability of wearable chemical sensors has hindered further progress towards continuous personal health monitoring. This is due to several key challenges that have yet to be successfully addressed, such as obtaining sensor response using low analyte concentrations and small sampling volumes of the biofluid and mechanical resiliency, biofouling, and biocompatibility of the sensors. The recent introduction of non-invasive wearable electrochemical sensors attempts to address these key challenges and fill major gaps in the wearable sensor technology.

Wearable non-invasive electrochemical biosensors

Similar to their *in vitro* counterparts, wearable non-invasive electrochemical sensors can detect target analytes in tears, saliva, sweat, and skin interstitial fluid. Researchers have recently made considerable efforts to develop wearable chemical sensors that can conveniently monitor these biofluids (Table 1).

Saliva-based sensors

Saliva is a complex biofluid comprising numerous constituents permeating from blood via transcellular or paracellular paths. Hence, sialochemistry offers an excellent non-invasive alternative to blood analysis for monitoring emotional, hormonal, nutritional, and metabolic state of the human body [6]. Saliva is also readily available compared to blood and requires fewer pretreatment steps. These virtues of saliva have attracted the attention of several researchers to develop portable *in vitro* salivary diagnostic tools [7].

The field of wearable salivary sensing has experienced considerable progress, aimed primarily towards the incorporation of sensors within partial dentures. The first examples of such wearable sensors were demonstrated already in the 1960s for monitoring mastication. Plaque pH is a useful parameter for studying plaque acidogenicity [8], whereas monitoring fluoride activity informs an individual about the fluoride dentifrice efficacy. Denture-based devices were thus modified to continuously monitor pH [9] and fluoride activity [10] in saliva and dental plaque (Figure 1A). These potentiometric sensors were fabricated by incorporating liquid junction-based electrodes, miniature transmitters, and a power supply. Although these sensors provide continuous real-time detection, they face several limitations, particularly the replacement of several teeth by the sensors and the possibility of leakage of the internal solution. Additionally, the pre-calibration step adds extra work-load for the user. Temperature variations affect the response of potentiometric sensors and hence require the incorporation of temperature sensor for compensation. Minamitani *et al*. [11] addressed some of these issues by integrating a temperature sensor and liquid junction-free iridium oxide pH electrode on a denture base. Such a device can be miniaturized and easily worn by an individual without the need for replacing teeth.

An ideal salivary sensor must conform well to the complex anatomy of the mouth with minimal inconvenience to