Non-Invasive Wearable Sweat and Tear-Based Biosensors for Continuous Health Monitoring

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Abstract. Over the years, the continuous advancements within the wearable biosensor field have raised public awareness in exploring new strategies for people's personalized point-of-care testing. Biosensors are multifunctional devices that allow people to quantify a range of biological signals through highly sensitive and small-scale sensing platforms, thus providing users convenience when limiting the need for clinical check-ups and laboratory diagnosis. Via dynamic, non-invasive evaluation of biomarkers in bodily fluids, biosensors are able to provide users with a nearly instant numerical result of the targeted biomarker's level (e.g., glucose, chloride) within their body. Here, this paper mainly focuses on exploring the wide range of sweat and tear-based biosensors' applications and methods to some extent. New generations of sweat-based wearable biosensors have been developed to better monitor one's health status by introducing techniques such as microfluidic sweat collection and Iontophoresis sweat induction methods. Additionally, much investment and effort have been put into developing tear-based wearable biosensors. For example, contact lens-based sensors are the most commonly adopted method for tear analysis, providing a minimally invasive detection of biomarkers.

Keywords: Health monitoring; Tear-based biosensor; sweat-based biosensor; wearable biosensor.

1. Introduction

Biosensors are analytical tools that exploit molecular cues from analytes to generate quantitative or qualitative data. The biosensing notion first emerged in the early 1900s, with the acid concentration in solutions being proportional to the electrical current across the membrane [1]. However, in 1956, Leland Clark developed a 'true biosensor device' for detecting oxygen [1]. In the past few years, wearable bioelectronics has received vast attention worldwide due to their potential for predictive medical modeling, providing continuous, real-time physiological information and thus allowing personalized point-of-care testing. Earlier accomplishments in this field have primarily centered on biosensors that track movement and vital signs, including heart rate, body temperature, calories burnt, and steps [1]. Nevertheless, in the last few years, numerous researchers have taken a step further in trying to conquer major challenges in healthcare applications. For example, managing chronic diseases like diabetes or remote health monitoring for elders in the community.

The constantly rising pace of newly disclosed proof-of-concept research and the many successful commercially available ones, especially a range of glucose monitors that can now be seen often in real life, all indicate that the wearable biosensor market is rapidly expanding. However, some products still demand further large-scale validation studies, including increased accuracy, precision and the necessary device regulatory methods in the market.

Non-invasive wearable biosensors can be used for bodily fluids including sweat, interstitial fluid, saliva, and tear and breath analysis. Biofluids are vital human resources that contain valuable biomarkers such as electrolytes, metabolites, heavy metals, cytokines, hormones and amino acids, which could provide insight into one's physical well-being and thus give flexibility and versatility in one's health monitoring (Figure 1) [1]. Wearable biosensors comprise three basic parts, the receptor, the transducer, and the signal amplifier [2]. The biorecognition component (e.g., enzyme, antibody, cell receptor, or organelle) situated on a transduction platform can initially detect the target biomarker [2]. Then, a signal that a transducer can detect will be generated, and thus after signal processing, the result can be converted to displayable data, which users can read easily [2].

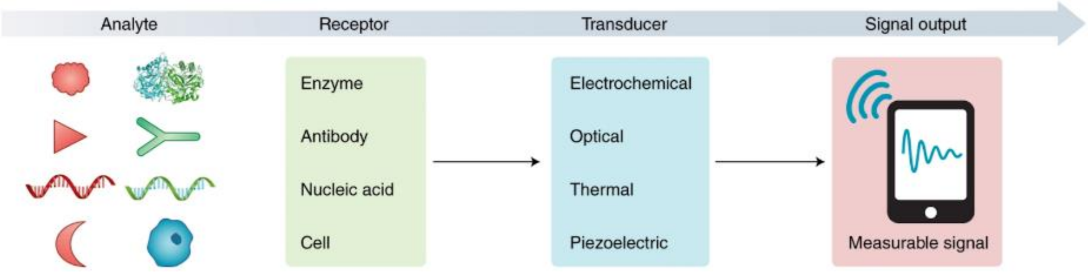

Fig. 1 Schematic representation of biosensor operation principles [1].

2. Diverse Applications Towards Healthcare Monitoring

2.1 Sweat-Based Biosensors

Wearable sweat-based biosensor provides considerable potential in enabling continuous health assessment as sweat glands are distributed on human skin at around 100 to 200 glands per centimeter squared [1]. Additionally, a variety of substances are found in sweat, including metabolites like lactate, glucose, and cortisol; electrolytes like sodium and chloride; low concentrations of trace elements like zinc and copper; as well as low concentration of large molecules like proteins, cytokine, and neuropeptides [1]. However, as the secretion volume of sweat is low and its evaporation rate is high, the sweat sample collection may be a foresee burden for researchers [3]. Hence, these biosensors generally require higher selectivity and sensitivity than traditional analytical methods used for bodily fluids such as blood samples, considering decreased biomarkers (*e.g.*, lactic acid and glucose) in sweat samples [3]. The following sections discuss previous research on different sweat induction and collection methods.

2.1.1 Microfluidic-based sweat collection method

In this method, sweat is directly captured from the skin and transported through microfluidic channels, reservoirs and separators employing the capillary action linked with sweat generation [4]. This method aims to minimize evaporation, contamination and dilution of the fluid sample to enhance the ability for the collection of sweat, which this technique is also suitable for in situ analysis [5]. Additionally, to strengthen capillary force, the microchannels are often combined with a layer of porous hydrophilic structures like sponges or cellulose papers that can store or absorb sweat produced [6]. Yang and their co-workers developed a microfluidic sweat biosensor for continuously monitoring tyrosine and uric acid, which are analytes associated with metabolic disorders and gout [7]. This sensor comprises a multi-inlet microfluidic module; a graphene-based chemical sensor for uric acid detection due to its outstanding electrochemical properties of high current density, large surface area and high electron mobility; and additional physical sensors to monitor the user's skin temperature and respiration rate simultaneously. Therefore, this system of sensors can ensure an abundant evaluation of the subject of interest [7]. Furthermore, a CO_2 laser-cutting method is adopted to fabricate the above units onto a polyimide sheet [7] (Figure 2).

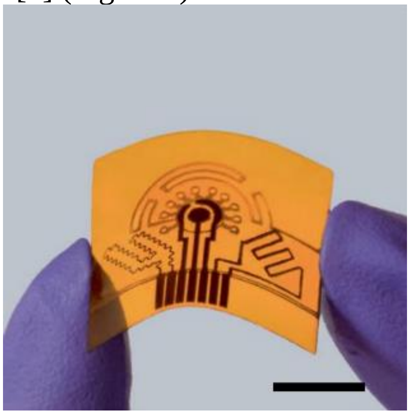

Fig. 2 Photograph of a bent skin patch. Scale bar, 1 cm [7].

Concerning patient usage, this sensor can be placed on different parts of users' skin, connected to a wireless unit and transmit data via Bluetooth to an electronic device that displays numerical results [7] (Figure 3). Experimental trials showed a promising result of this sensor as the dynamic fluctuations of sweat uric acid detected by the wearable sensor before and after a purine-rich diet is shown to closely resemble those of serum uric acid, though slightly higher with the data points [7] (Figure 4 and Figure 5).

Fig. 3 Photographs of a subject appealing to the biosensor on different body areas while exercising [7].

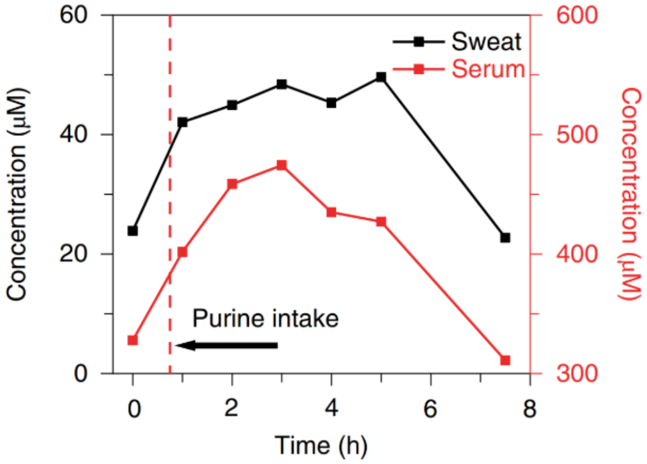

Fig. 4 Sweat and serum uric acid levels' dynamic variation before and after a purine-rich meal for 7 hours [7].

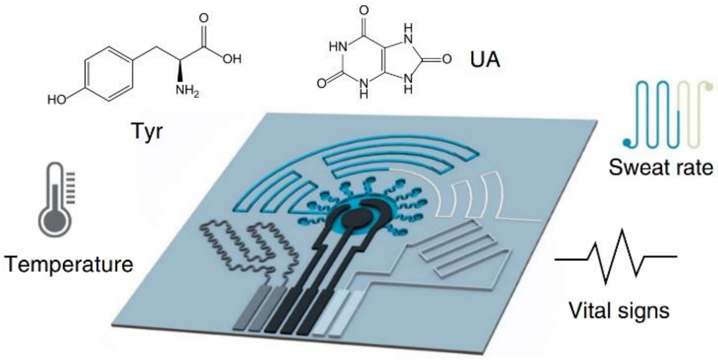

Fig. 5 Multiplexed sensor patch for sensitive sweat uric acid, tyrosine detection, and other vital-sign evaluation [7].

2.1.2 Iontophoresis-based sweat induction method

Another commonly used technique for sweat-based sensors is the Iontophoresis-based sweat induction method. Iontophoresis involves passing a low current through a hydrogel layer to deliver drugs, such as pilocarpine, across the skin. The medication stimulates the cholinergic eccrine glands and allows for sweat production at its equilibrium composition [2] (Figure 6). More specifically, at the anode of the patch, there is a screen-printed iontophoretic component capable of electrically inducing the sweat-stimulating drug to the epidermis at an applied current of around 0.6 mA (0.2 mA cm^{-2}). Hence, this drug can result in a temporary production of sweat of approximately 5 mins in total [5]. An additional screen-printed insulator may be incorporated into the anode electrode to confine the electrodes and contact areas [5]. As a method that obviates the need for intense exercise or heat exposure by chemically inducing sweat and then followed by a rapid analysis, this method can be more convenient for elderly or disabled people than the previous microfluidic-based sweat collection method. However, compared to sweating caused by those traditional sweat induction methods, sweating due to iontophoresis only lasts for a minimal period [5].

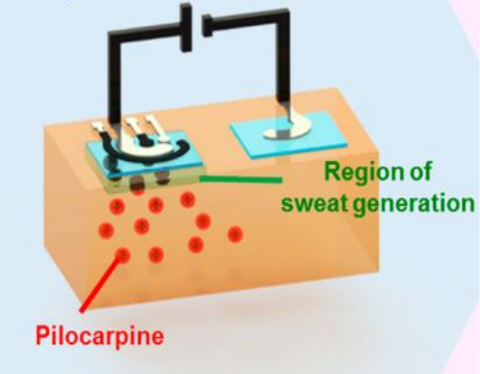

Fig. 6 Schematic diagram of the iontophoretic system and its components [1].

2.2 Tear-Based Biosensors

Tear is a vital source of biomarkers, and it resembles close tear-to-blood concentration correlations as its component is diffused directly from blood [8]. Additionally, the tear is a less complex source than blood which signifies it provides a non- or minimally invasive platform for biosensing and detecting specific molecules [8]. Human tears, or lachrymal fluid, contain a wide range of different-sized compounds, including peptides, proteins, metabolites, electrolytes and alike, which are especially crucial for monitoring specific ocular diseases (*e.g.*, dry eye syndrome, trachoma) [9]. To date, glucose is one of the most commonly studied analytes targeted for detection in tears, as tears' glucose level has been found to closely resemble those of blood, with a lag time of around 10 minutes [9]. Hence, tear-based glucose biosensors may provide alternatives to the good old finger pricking way of monitoring one's glucose level [9]. Currently, the most significant challenge when extracting tear fluid for a numerical result is that even a small stimulation or irritation might trigger a rise in tear production, which could compromise the biomarker's concentration [8]. Potential solutions towards this issue include less invasive capillary collection methods at the canthus to calibration with continuous monitoring devices such as electrode-embedded contact lenses [9].

As a great platform for tear analysis, contact lens sensors were first established using optical methods to monitor the glucose level in tears [10]. This method can detect the fluorescence of concanavalin A and phenylboronic acid derivatives that competitively bind with glucose [10]. Furthermore, the Parviz team adopted an electrochemical contact lens sensor method to enhance the sensor's sensitivity, linearity and accuracy [11,12] (Figure 7). By utilizing supplementary control (GO_x-free) working and counter electrodes in a dual sensor configuration, researchers could eliminate interference problems caused by other biochemicals [11,12]. The incorporation of a wireless readout chip (2.4 GHz) and the use of far-field electromagnetic radiation (3 µW with a distance of around 15 cm) to power the device has advanced contact lens sensors since that time [12]. As a result, this system makes promises to eventually use mobile phones' near-field communication feature for a point-of-care purpose [12].

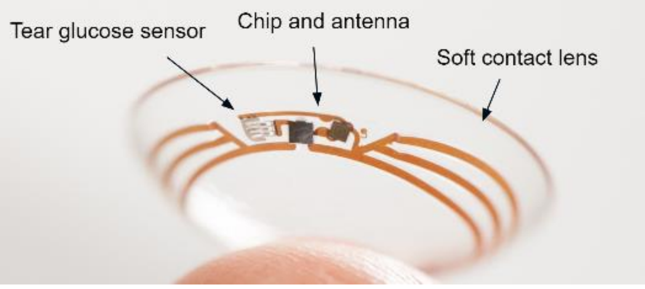

Fig. 7 Tear glucose contact lens sensor formerly under testing by Novartis and Google. (adapted from https://blog.google/alphabet/introducing-our-smart-contact-lens/)

3. Conclusions

This paper highlights that many innovative wearable biosensors have already been proven practical in various applications with detecting diverse biomarkers (*e.g.*, metabolites and electrolytes) in different bodily fluids. These studies have demonstrated that wearable biosensors have tremendous promise for real-life applications. Here, wearable biosensors showcase a non-invasive sensing approach that provides convenience and simplicity for patients or users while maintaining accuracy as they count on specific biomarkers instead of relying on observable symptoms of the subject. Hence, these sensors may be able to substitute costly and time-consuming laboratory testing in many cases. Furthermore, it may eliminate the random errors arising from laboratories' sample storage, as most wearable biosensor sensing methods adopt an immediate electrochemical analysis of the bodily fluid sample. Most importantly, wearable electronics provide real efficiency to users as they can monitor their health digitally whenever and wherever they want. Conversely, as the design of these biosensors is limited due to their size and material restrictions, their data accuracy and precision may still require slight enhancements compared to other conventual analytical technologies.

Recent technological advances suggest that wearable biosensors may be employed in disease monitoring, exercise intensity evaluation, etc. But despite recent advancements in wearable sensors, the latest technologies in this sector have only proven wearable biosensing platforms for a limited number of biomarkers, and very few steps were taken toward commercial applications.

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