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IMPACT OF BIOMEDICAL SENSORS IN HEALTHCARE MONITORING

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Abstract

An investigation was conducted on the latest advancements in wearable flexible sensors (WFSs) designed for the detection of sweat analytes. Recent progress has shown the creation of sensor systems that are integrated, mechanically flexible, and capable of multiplexing. These systems also include on-site electronics for signal processing and wireless data transfer. Compared to sensors that just measure one substance, these devices provide a chance to analyze substances that are influenced by other factors (such sweat rate and pH) with more accuracy. This is achieved by enhancing the calibration process via real-time analysis in the actual environment, all while keeping the device lightweight and easy to wear. Integrated wearable devices can monitor important health parameters and distribute medications as needed. However, before these systems can be used in clinical applications, it is necessary to verify the connection between sweat and blood readings via in vivo validation testing. Enhancements are required to enhance the sensitivity, precision, and consistency of the device in order to provide more dependable and customized continuous measurements. Recent advancements in non-invasive wearable biosensors for sweat analysis have merely scratched the surface of their potential for health monitoring. Further considerable progress is expected to be achieved in the medical area.

1. Introduction

Sweating, often known as perspiration, is a process of thermoregulation in which the sweat glands of the typical adult human release between 500 and 700 ml of hypotonic fluid every day, under most climatic circumstances [1]. Sweat is readily obtainable from the skin surface of the human body. It is produced by the eccrine glands and contains valuable physiological information, including electrolytes (such as sodium and potassium ions) and metabolites (such as lactate and glucose) [2,3]. The ease of accessing sweat makes it a valuable biofluid as it can be collected using non-invasive techniques, unlike other biofluids like blood [4].

Biomarkers present in sweat may be used to identify hereditary abnormalities, such as cystic fibrosis in babies, by examining high chloride levels [5,6]. Additionally, these biomarkers can be employed to detect illnesses associated with cystic fibrosis resulting from salt loss [4]. Moreover, researchers have discovered a connection between the levels of glucose in sweat and blood, which could be utilized for continuous monitoring of diabetes [7]. Additionally, the measurement of lactate can be employed to detect the presence of ischaemia [8]. Furthermore, the temperature of the skin surface can offer valuable insights into a range of skin injuries and diseases [9].

The analysis of sweat biomarkers has mostly been accomplished by the use of electrochemical sensing using biosensors. A biosensor is an analytical instrument used to provide instantaneous data (such as concentration) of one or more chemical components (analytes) in a sample [10]. The idea was first developed in 1962 by Dr. Leland C. Clark, with the objective of analyzing blood glucose levels using a 'enzyme electrode' [11]. Currently, modern biosensors continue to adhere to the same structure as Dr. Clark's initial model, which consists of a recognition stage (including the analyte and a sensing device) and a transduction stage [10,12].

Previous research using biosensors have encountered many limitations in the collection and analysis of sweat for disease detection. These limitations include ineffective sweat collection techniques, the need for distinct phases of collection and analysis, and the difficulty to monitor numerous analytes concurrently [13–15]. In addition, there is a dearth of correlation verification between sweat and blood measurements utilizing in vivo validation studies. So far, ethanol is the only analyte that has been validated by this approach [16]. The limitations mentioned are now being tackled due to the latest developments in integrated sensor arrays in wearable electronics [3,17]. This review aims to examine the latest advancements in wearable electronics for detecting diseases through sweat. It will critically analyze the application and production of these devices, and quantitatively compare their sensor performance parameters, such as sensitivity, limit of detection (LoD), linear range, and accuracy, with traditional metrics.

2. Sweat as a biological fluid

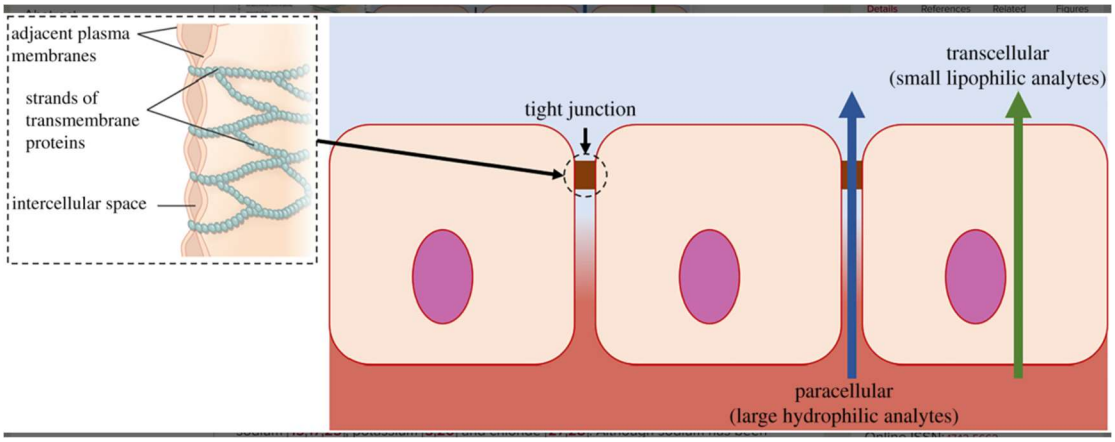
Until recent years, research on wearable sensing for eccrine sweat has been somewhat neglected. The advancement of sensors that have integrated sweat stimulation for continuous sweat access [18,19], along with multiplexed sensing arrays for in situ calibration of analyte measurements [3,20], has led to the emergence of sweat sensing as a technology that can provide continuous access and monitoring of analytes, using a non-invasive platform. In the last 5 years, there has been a significant rise of nearly 10 times in scholarly publications related to sweat sensing due to these improvements [16].

The biomarkers that may be detected in sweat have previously been extensively studied; however, the clinical use of many of these substances for monitoring health conditions has not yet been shown. Lipophilic analytes, which are small and hydrophobic, such as steroid hormones (cortisol [13], testosterone [21], etc.) and medicines (methylxanthine [22], levodopa [23], ethanol

[16], etc.), show a significant association between the quantities found in sweat and blood. These biomarkers can pass through cell membranes by partitioning transcellularly. However, larger or more hydrophilic analytes may enter sweat through a paracellular route, active channels, or vesicular/exosomes. This can make it difficult to establish a correlation between sweat and blood (Figure 1) [21].

Figure 1. The process by which analytes move from interstitial fluid and blood to sweat via lipophilic cell membranes [24].

The increased number of cellular barriers at tight junctions results in a higher amount of filtration, leading to greater dilution of bigger biomarkers. An instance of this phenomenon may be seen in the case of sweat glucose, which is conveyed via a paracellular route and is around 100 times less concentrated than interstitial fluid or blood plasma glucose [7]. The significantly reduced concentration poses a significant obstacle in the field of wearable sweat sensing,



highlighting the need for very sensitive and highly specific devices with meticulously crafted sweat sample techniques.

Electrolytes, including sodium [15,17,25], potassium [3,26], and chloride [27,28], are the most frequently measured substances in sweat. While salt has been shown to be a valuable indicator of electrolyte imbalance [15], there is no indication of any association between sodium levels in blood and sweat [13]. However, there is new evidence suggesting that sweat sodium might be useful in determining the correlation between regional sweat levels and overall fluid and electrolyte loss in the body. This is achieved by adopting personalized wearable monitoring, which has demonstrated a close 1:1 match between observed and anticipated whole-body fluid losses [29]. The relationship between blood and sweat potassium has not yet been shown, since even little variations in blood potassium levels are overshadowed by interference sources when measuring sweat potassium [21]. Research has shown that measuring sweat chloride levels can be used in point-of-care testing for cystic fibrosis [5].

3. Wearable sensors designed to detect and measure perspiration

There are two main categories of sensors: flexible [30] and non-flexible [31]. In order to effectively collect and analyze physiological data from sweat, the sensor has to be in direct touch with the skin. It should be able to withstand movement and activity while staying comfortable to wear. Therefore, in order to accommodate the curved nature of human skin, wearable flexible sensors (WFSs) are the ideal choice [31]. Recent developments in WFSs have included embedded and integrated signal processing circuits to enable real-time data analysis and wireless transfer to a computer or smart device [3,33]. Traditionally, Bluetooth has been used for transmitting data wirelessly because it offers advantages such as cheaper installation costs, excellent interoperability, and less hardware needs compared to other network protocols like Wi-Fi or ZigBee [34]. Figure 2 depicts a diagram showing the integration of signal processing and wireless transmission in a WFS system.

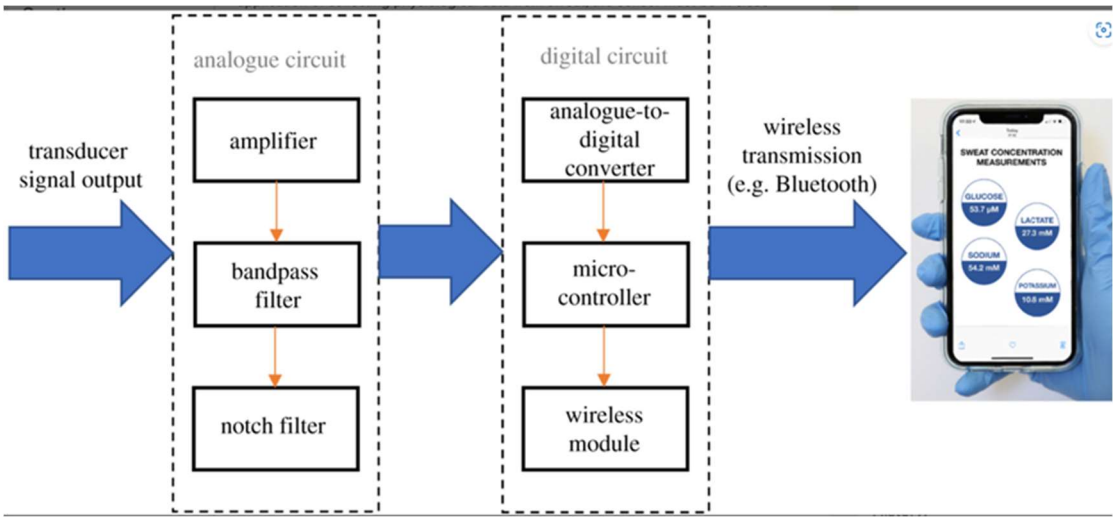


Figure 2. Diagram illustrating the processing and transmission of the transducer output signal to an external monitoring device [33].

4. Software programs or computer applications

Currently, wearable biosensors are mostly used in the field of point-of-care medical or physiological monitoring. They serve the purpose of detecting illnesses and health issues in a more convenient and less intrusive way compared to traditional monitoring approaches. WFSs have been widely used in recent years to identify analyte concentrations that are pertinent to illnesses and health problems. Nevertheless, these non-invasive techniques have often been deficient in their ability to detect many analytes simultaneously and lack on-site circuitry for in-situ analysis and calibration.

Gao et al. [3] have transformed the field of sweat biosensing by developing a wearable integrated sensor array that allows for the simultaneous measurement of numerous analytes. This is achieved via the use of a flexible integrated sensing array (FISA) and the analysis and transmission of data using a flexible printed circuit board (FPCB). In figure 3a, the FISA and FPCB, which are made on a flexible PET substrate, are shown on a person's wrist. The FISA is

about the same size as a US quarter dollar coin, with an area of 25 mm2 [3]. The substances analyzed in this investigation were metabolites (glucose and lactate) and electrolytes (sodium and potassium). This technology enables real-time physiological monitoring during exercise, providing visual output of the subject's status on a smart device. This data may serve as an indicator for disorders such as hypoglycemia caused by diabetes mellitus, pressure ischemia caused by lactate, hypokalemia caused by potassium, and hyponatremia caused by sodium.

The device was used to capture measurements when it was placed on the forehead, arm, and wrist during cycling activity (figure 3b). The data collected from the device were compared to data analyzed later, which were obtained from a different source, and showed remarkably similar patterns (figure 3c). Nevertheless, the concentration of glucose was shown to decrease after prolonged activity as a result of the dilution of glucose in sweat over time. Furthermore, distinct glucose concentrations were recorded by the devices at various sites on the body. A proposal was made suggesting that the activity of the glucose oxidase (GOx) enzyme is affected by rising temperature during exercise. Therefore, it is necessary to closely observe and analyze the pace and composition of sweat, as well as environmental factors, in orders to accurately monitor the link between perspiration and blood glucose levels. In addition, although there was a link between the sweat rate and important biomarkers, no association was found between sweat glucose and blood glucose concentrations.

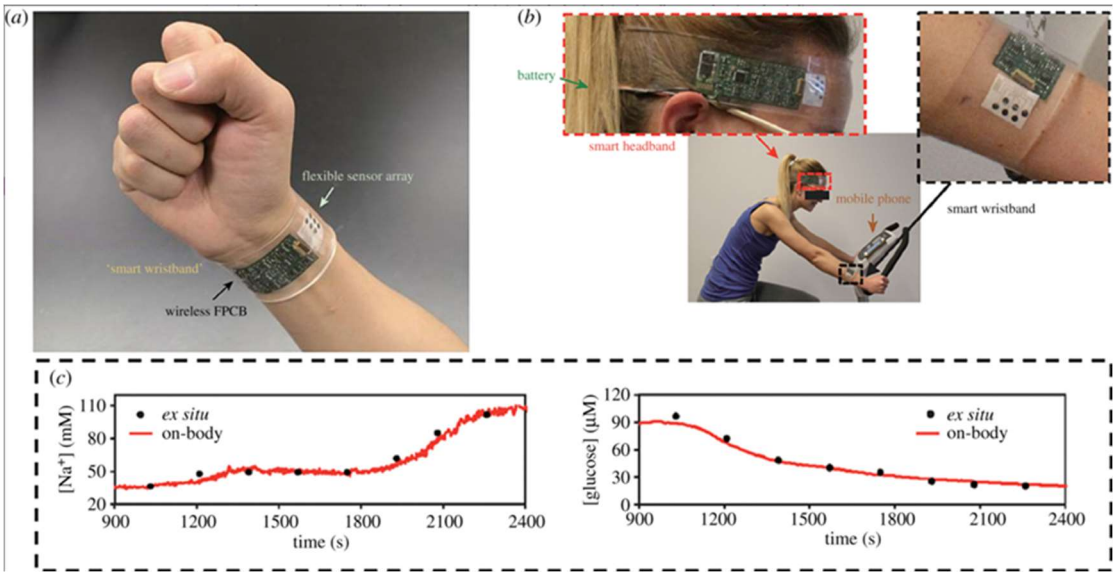


Figure 3. (a) The FISA and FPCB are worn on the wrist; (b) the sensor array is worn on the forehead, arm, and wrist during cycling activity; and (c) the analysis conducted on the body produced data for sodium and glucose that were extremely comparable to the analysis conducted outside the body [3].

5. Conclusion

This study examined the most advanced technology in wearable biosensors for detecting substances in human perspiration that are important for monitoring diseases and health conditions. Extensive research has been carried out in recent years to develop methods for analyzing sweat analyte concentrations in a non-invasive, in situ, and real-time manner. Progress in manufacturing methods and material science has enabled the integration of several sensors into a single mechanically flexible system. This system also includes on-site electronics for signal processing and wireless data transfer. These devices provide a chance to more accurately adjust analytes that rely on other factors, such as the relationship between perspiration rate and glucose levels.

The combination of customized materials has been shown to be advantageous in improving the capabilities of sensors, including higher sensitivity, lower limit of detection (LoD), and a wider linear range. These improvements are achieved by increasing the surface area and porosity of electrodes via modifications such as nanofibers and nanoparticles. Introducing conductive nanoparticles into non-conductive materials by doping has been shown to be beneficial for creating non-enzymatic electrochemical sensors. These sensors exhibit greater limits of detection (LoD), sensitivity, and stability compared to enzymatic sensors, mostly because of their increased specificity.

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