Emerging wearable technologies for personalized health and performance monitoring

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ABSTRACT

Wearable sensor technologies provide continuous insight into the body's physiological state and enable real-time feedback for timely intervention. Therefore, they play a critical role in the evaluation and improvement of the health and performance of individuals. Currently, commercialized wearable technologies are only capable of tracking physical activities and vital signs, and fail to unobtrusively access molecular-level information related to the body's dynamic chemistry. To this end, sweat-based wearable biomonitoring is one of the most promising candidates to merge this gap. Sweat is a rich source of physiological information that can be retrieved non-invasively. It contains many critical analytes, which can be partitioned from blood with some degree of correlation. Therefore, in principle, sweat analysis can be used to provide non-invasive proxy measures of target biomarkers in blood for various clinical and physiological applications. Recent advances in electrochemical sensor development, flexible device fabrication and integration technology, and low power electronics have enabled the development of wearable sweat biosensors. However, despite such progress, the barrier to sweat-based health monitoring continues to be the inability to accurately infer physiologically relevant information from sweat measurements to enable actionable feedback. Here, we briefly review the significance of sweat-based monitoring and recent advances in sweat sensing technologies.

Keywords: Wearable technologies, electrochemical sensors, personalized medicine

1. INTRODUCTION

1.1 Wearable health monitoring: current status and unmet needs

By monitoring an individual's physiological state on a real-time basis, wearable technologies are vital to the actualization of personalized medicine. Specifically, wearable molecular diagnostic platforms with real-time biomarker molecule sensing and information transmission capabilities can facilitate a variety of clinical applications including large-scale clinical investigations, remote patient monitoring, disease prevention/management, and pharmaceutical monitoring. The transmitted information can be used by both users and caregivers to implement preventive and corrective medical action in a timely manner [1-5]. Examples of medical applications include: (a) an emergency situation where critical diagnostic information may call for an immediate alternative treatment plan, (b) a hospital inpatient setting where instantaneous data analysis can be autonomously and passively retrieved, (c) an outpatient setting where the health status of the patients can be remotely monitored, or (d) well-being monitoring to inform lifestyle choices.

Conventional diagnostic methods are not amenable for wearable monitoring. They often require a blood sample, which is invasive and costly, provides limited discrete data points, requires user intervention, and may need sample pre-treatment [1,2]. The challenge remains to devise a wearable technology that can non-invasively, autonomously, and continuously sample and analyze biofluids and correlate the readings to the health status of individuals [3]. Currently, commercialized wearable technologies are only capable of tracking physical activities and vital signs, and fail to unobtrusively access molecular-level information related to the body's dynamic chemistry. To this end, sweat is a promising biofluid to target for clinical analysis. Sweat is a rich source of molecular-level information and contains a large panel of biomarkers spanning from metabolites (*e.g.* glucose, lactate, and pyruvate) and (non-) metal ions (*e.g.* sodium and potassium) to large molecules (*e.g.* proteins) [1-4]. The concentration gradient between plasma and sweat allows for passive diffusion of molecules into sweat. Several studies have shown that sweat and blood compositions are to some degree correlated, and thus the sweat readings can be used as proxy measures to track the health status of individuals [4]. Various challenges need to be resolved in order to make sweat-based sensing a reliable method of health monitoring. This includes on-demand stimulation of sweat secretion in sedentary individuals to make sweat accessible,

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as well as the development of sensing interfaces that can be incorporated into wearable formats and can retain their functionality for prolonged periods of time.

1.2 Molecular diagnostic based on sweat analysis

The primary objective of sweat-based diagnosis is the appropriate identification, validation, and detection of clinically and physiologically informative biomarkers. Sweat contains a large panel of small molecules (<1-15 kDa) that originate in metabolic pathways. The most common metabolic biomarker analyzed in sweat is glucose, which potentially has a significant informative role in diabetes management and prevention. Glucose concentrations in sweat have been shown to correlate with blood glucose levels when sweat is properly stimulated and collected [4]. Lactate information in sweat is also of interest for a variety of clinical applications as it is a function of sweat gland energy metabolism. Unlike the case for sweat glucose, where the present glucose molecules are mostly originated from blood, the lactate found in sweat is primarily due to the product of gland metabolism [4,5]. In this regard, lactate levels in sweat can be used as an indicator of sweat gland activity and the body's thermoregulation capability. Moreover, the measurement of electrolyte concentrations in sweat is potentially useful for a variety of applications including hydration monitoring. In the context of Cystic Fibrosis (CF, a genetic disorder), the abnormally high concentration of electrolytes (specifically chloride) is used as a tool for diagnosis. Additionally, a large panel of hormones and neurotransmitters (including vasoactive intestinal peptide, neuropeptide Y, substance P, and calcitonin-gene-related peptide) are present in sweat, which can provide insight into the activity of the central and peripheral nervous systems.

1.3 Accessing sweat biomarkers

The majority of the demonstrated wearable sweat analysis platforms rely on exercise-based sweat induction to access sweat biomarkers. However, this method of sweat induction cannot be scaled for general population health monitoring, because it requires intense and continuous physical activity to achieve relatively large sweat production for robust analysis [1]. Therefore, this mode of analysis is practically confined to athletic and physical activity performance monitoring applications. In order to make sweat accessible on-demand, iontophoresis can be exploited, which involves the use of electrical current to deliver secretory agonist molecules underneath the skin for sweat secretion stimulation [5]. Recently, Emaminejad *et al.* reported an electrochemically enhanced iontophoresis interface, integrated in a wearable sweat analysis platform, which can be programmed to induce sweat with various secretion profiles for real-time analysis [5]. In another study by Kim *et al.*, an iontophoresis-based sweat induction method was employed *for in-situ* sweat alcohol sensing [6].

1.4 *In-situ* electrochemical analysis of sweat biomarkers

Electrochemical sensing methods are suitable for sweat analysis as they allow for the measurement of target biomarker molecules with high sensitivity and selectivity in a wearable format. The electrochemical sensing interface consists of 1) a biological recognition element (*e.g.* an antibody, enzyme, or nucleic acid) that can specifically interact and recognize the biomarker of interest and 2) a transducer that can convert the resultant biochemical interactions into measurable signals. From a practical standpoint, these sensors must withstand prolonged operations on-body while preserving their sensitivity [2,7]. The choice of the electrochemical sensing interface method depends upon the molecular properties and concentration range of the target biomarker in sweat. For example, the most commonly measured sweat electrolytes are in the millimolar range and are measured with the aid of ion-selective electrodes (ISEs), while metabolites such as glucose and lactate, which are in micro- to millimolar range, are measured using enzymatic interfaces [5]. For the quantification of electrolytes, potentiometric analysis methods are used in conjunction with ISE electrodes, which output voltage levels that are logarithmically correlated to the concentration of the target ions in the solution. For the quantification of metabolites, amperometric analysis methods are used in combination with electrodes that are functionalized with enzymes, which output electrical current levels that are linearly proportional to the concentration of the target metabolites [5,7-9].

Detection of low-concentration biomarker molecules, which are in the sub-micromolar range, is challenging due to the presence of interfering species and the limited sensitivity of the demonstrated wearable sensors. To address this, new classes of affinity-based electrochemical biosensors are currently being explored. These sensors rely on the capture of a target analyte by biomolecules that have been immobilized on the sensor surface. Antigens and antibodies have been the most widely utilized probe biomolecules for construction of such sensors. However, the key challenge is preserving the biochemical integrity of these capture probes for on-body sweat analysis. For example, Prasad *et al.* developed a sensing strategy for the detection of IL-6 based on ZnO-thin-film-functionalized immunoassays [10]. Room temperature ionic liquids were used to construct the sensing interface to ensure prolonged, stable sensing. Moreover, electrochemical immunosensors have shown to be promising for the detection of hormonal biomarkers such as cortisol in sweat. A non-faradaic, label-free cortisol biosensor was constructed using MoS_2 nanosheets patterned on a flexible substrate, where cortisol antibodies were used as probe molecules to capture cortisol molecules [11].

To ensure the accuracy of electrochemical sensor readout, *in-situ* calibration strategies may be needed. For example, in the context of enzymatic based sensors, the increased temperature on skin may lead to an increase in enzyme activity and a larger generated electrical signal for a given concentration of target analyte. Specifically, Emaminejad *et al.* demonstrated that not compensating for increased temperature may lead to the overestimation of sweat glucose and lactate concentrations [7]. In addition to temperature calibration, calibration with respect to the sweat pH level may be necessary as pH may also affect the sensor readout. As the sweat pH level is dependent upon the secretion rate, the variability of the secretion rate may affect the acidity of the sensing medium and alter the activity and binding properties of the sensor receptor elements [2].

1.5 Electrochemical Sensor Integration with Fluidics and Electronics

Various methodologies have been used for integrated *in-situ* collection and analysis of sweat, including the use of absorbent pads, textile patches, and microfluidic housing with integrated biosensing functionalities. The mechanical flexibility of these substrates allows for establishing intimate contact with the skin for robust sensing and ensures the users' comfort in wearing such devices for an extended period of time. For example, a microfluidic-based device has been demonstrated that captures, routes, and stores sweat in separate regions for analysis [12]. The intended wearable operation of the device was validated successfully in the context of extended physical activity (bicycle racing).

Furthermore, one of the major challenges of wearable sensing is measurement artifacts from user motion and the presence of electromagnetic interference. In this regard, the integration of the transducer with readout circuitry is necessary to enable immediate and seamless analog/digital signal processing and wireless transmission. The readout circuitry in principle can be reduced to a single IC chip in mm-scale dimensions, however the IC development process is lengthy and costly, and is not amenable for prototyping to establish the required design specifications. Alternatively, commercially available discrete chips can be used to implement the system-level functionalities. The diversity of electronic functionalities may require the assembly of a substantial number of discrete chips and peripherals, leading to an increased size of the electronic system (beyond cm-scale). Therefore, from a practical standpoint, it may be essential to implement such electronic systems on flexible substrates. In this regard, Xu *et al.* demonstrated an implementation of a wearable microfluidic system that uses a thin elastomeric enclosure where electronic components are connected with the aid of free-floating interconnects [13]. The components selectively bond to cylindrical features on the elastomeric substrate for support and the microfluidic enclosures are designed in such a way to reduce mechanical stress on the device. This method allows devices to be designed to have the same basic characteristics (*e.g.* moduli, thickness, and elasticity) of skin for better contact and integration. Additionally, Emaminejad *et al.* [7,14] demonstrated a mechanically flexible electronic system, where the electronics were assembled onto a flexible printed circuit board (FPCB). This system implements five measurement channels (two amperometric, two potentiometric, and one for temperature sensing) with the aid of more than 10 IC chips and its functionality was validated in the context of multiplexed analysis of sweat biomarkers. As a follow up to this work, the same methodology was applied to integrate iontophoresis functionality in order to realize an autonomous and fully-integrated sweat extraction and analysis platform [5]. The clinical utility of the platform was validated through the diagnosis of cystic fibrosis and the investigation of metabolic correlation of glucose in sweat *vs.* blood.

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