

# Enzyme-Free Electrochemical Sensor for Wearable Sweat Biomarker

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**Abstract**—Sweat contains a wealth of health-related biomarkers, which has been a promising resource for personalized real-time monitoring at molecular level. Emergence of non-enzymatic electrochemical sensor that simulates the enzyme catalysis utilizing the functional material further promotes the development of wearable sweat sensor. Thus, there is an urgent need for centering on the regulation of the nanostructure, combination and preparation method of functional materials to enhance the catalytic activity for enzyme-free detection of sweat biomarkers. This aims to present the superiors of enzyme-free sensing on wearable sweat sensor, and provides guidance for material innovation, sensor design and system integration.

**Index Terms**—Aptamer, Chemisorption, Deprotonation, Molecular Imprinting Technique

## I. INTRODUCTION

Analytical devices for biomarker detection represent a rapidly advancing interdisciplinary field poised to revolutionize healthcare, including disease diagnosis, fitness management, and personalized medicine. Wearable sensors, in particular, have become indispensable tools in modern health care due to their ability to continuously monitor vital physiological parameters. By enabling the in-situ collection and real-time detection of vital biomarkers directly from body fluids, wearable sensors can capture valuable and seamless insights into the health status of individuals without the need for frequent hospital visits. Wearable sensors facilitate the development of personalized healthcare as they can continuously and closely monitor the levels of an individual's biomarkers. The long-term wellness tracking is conducive to the early disease diagnosis and treatment, holding great promise in biomedical field. The popularize of wearable sensors plays a crucial role in relieving the tense

medical resources due to the features of portability and instant test. As an ideal detection platform, realization of wearable sensing is often on the basis of regarding body fluids (e.g., saliva, tear, interstitial fluid and sweat) as the electrolyte, which ensures that the testing process can be conducted in an on invasive and in-situ manner. In addition, a wealth of health-related biomarkers existed in body fluids, such as metabolites, electrolytes, proteins, et al., have laid the foundation for the diagnosis of most diseases.

## II. OVERVIEW

Among the important body fluids, sweat is particularly attractive due to the simple sample collection and convenient storage. Unlike other wearable sensors that are only placed at the fixed position, sweat sensors can be attached to the random part of the body for detection, since sweat glands all over the body have the ability to secrete sufficient sweat as a test sample. In order to accelerate the sweat gland secretion rates, exercise, thermal and chemical stimulation are the three commonly used ways to induce sweating. But some researchers have reported that without the above stimulation methods, the sensor still gathers satisfied volume at the fingertip, due to the high-density distribution of sweat glands. In addition, absorbent pad, commercial Wescor Macro duct patch or microfluidic channel is usually used in conjunction with wearable sweat sensor to improve the efficiency of sweat sampling and transport.

Wearable sweat sensor for electrochemically tracking biochemical markers can be simply divided into enzymatic sensor and non-enzymatic sensor according to the used molecule recognition element. Emerging of non-enzymatic sensor promotes the further development of wearable sweat sensing, because of

the higher sensitivity, the longer operation time and the wider application range as compared with enzymatic sensors. These features allow for smooth detection of epidermal sweat, solving challenging problems such as enzyme assembly or low biomarker concentrations. Although a considerable number of reviews are completed in recent years to report the research progress of wearable sweat Sensors, the application of non- enzymatic electrochemical sensor in this field has not been summarized yet. Herein, we primarily focus on the recent advances of non-enzymatic electrochemical sensors in sweat analysis, and review material innovation, structure design, and system integration employed toward sweat sensing in the following sections. The sensing materials and electrolytes required for different types of molecular detection are mentioned in detail. In addition, sweat induction methods and microfluidic devices for sweat sampling and transport are introduced and discussed to show how these advances can improve the efficiency of sweat sensing. Finally, main challenges and opportunities for wearable sweat sensor toward personalized health monitoring are proposed.

#### *Non-enzymatic electrochemical sensor*

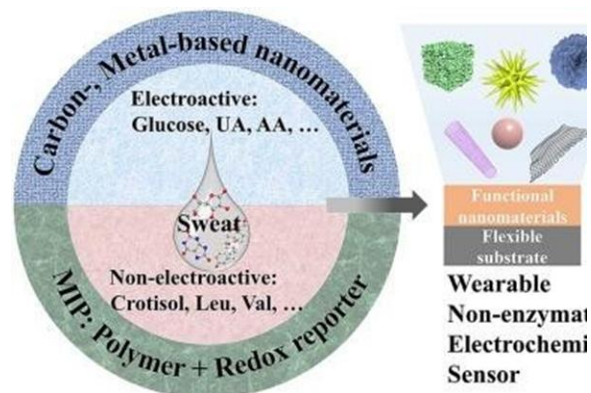
Traditional enzymatic sensors have good selectivity and high sensitivity owing to the specific recognition and excellent catalysis of enzymes. However, the enzyme not only is expensive, but also requires complex immobilization steps to maintain a constant signal in detection. Additionally, working environments (e.g., temperature, humidity and pH) are related to the enzyme activity closely, which restrict the application range of enzymatic sensors seriously. Despite in mild conditions, enzymatic sensors are also prone to performance degradation during use, thereby reducing the detection accuracy. Without the addition of enzyme, non-enzymatic sensors obtain the electrical signal through using the material on electrode surface to directly catalyze biomarkers. Independent on the temperature and humidity, the sensor demonstrates exceedingly strong tolerance to harsh environment in detection, prolonging the service life. Furthermore, the omitting of enzyme assembly in the sensor preparation prevents the enzyme dropping when the wearable sensor is deformed during physical activity. More importantly, the sensitivity of non- enzymatic sensor is much higher than that of enzymatic sensor, which means the possibility of trace analysis of low-content

molecules in sweat. Functional materials for identifying the biomarkers determine the response intensity of non-enzymatic sensors. Accordingly, high-active nanomaterials are increasingly developed to pursue the excellent electrochemical behaviors. With the development of nano-technology, the exploration of structural-performance correlation contributes to the further improvement of enzyme-free sensing. Interesting regular structures (flower-like, rod-shaped, flaky, clustered, etc.) are successively applied in the construction of non-enzymatic sensors. The researches on materials and structures provide enough means for sensing multiple components of sweat in the absence of enzyme. Based on the differences in molecular structure, there are two main components existing in sweat, namely electroactive (e.g., uric acid, ascorbic acid) and non-electroactive (e.g., hormones, some proteins) molecules. For enzyme-free detection of most electroactive molecules, either carbon-based materials or metal-based materials will produce an electric signal at optimal potentials. Nevertheless, of considerable note is that the sensing material or electrolyte used in certain molecular detection needs to be specially screened to achieve a satisfactory level. As far as glucose detection is concerned, Pt and Au are the only two nanomaterials that can oxidize glucose in neutral electrolyte without the addition of enzyme.

But in alkaline medium, metal-based nanomaterials having the ability to combine with hydroxyl ions to form peroxides are a better choice. It is very challenging to identify non-electroactive molecules in the absence of enzyme, aptamer or antibody, due to the lack of active sites in molecular structure. To this end, enzyme-free detection is performed by utilizing molecular imprinting technique in that case, which builds complementary cavities with the same size and shape as target molecules to obtain the corresponding signal.

Wearable sweat sensors for the electrochemically monitoring of biomarkers the components in sweat can be roughly divided into two categories: electroactive and non-electroactive molecules based on the molecular structure. For electroactive molecules, both carbon- and metal- based nanomaterials are served as the catalytic core for oxidizing the active group to achieve the electrical signal. However, it is worth noting that an optimal working potential determined by The functional material is crucial to obtain the

precise response, preventing interference of oxidizing other substances.



Compared with electroactive molecule, lack of the active group is a complication to detection of non-electroactive molecule, which means that simply adjusting the working potential by using the functional material is ineffective to realize the Direct electron transfer. At present, molecularly imprinted polymer (MIP) based sensor, aptamer sensor and immune sensor are the most comm. only used methods in the absence of enzymes. Among them, molecular imprinting technology is different, which does not need the addition of aptamer or antibody similar to enzymatic identification function, but only needs to build a cavity of non-electroactive molecule in polymer layer.

#### *Electroactive molecules*

Among electroactive molecules, glucose analysis as a separate part is described briefly because of the theoretical differences based on neutral and alkaline electrolytes. The functional materials used are required to regulate as the electrolyte changes.

Platinum and gold are the only two nanomaterials that can work in neutral medium according to the activated chemisorption model of Pletcher. Thus, Pt- and Au-based electrochemical glucose sensors have great potential in sweat sensing system. Lee et al. proposed a wearable sensor based on the Nano porous gold (NPG) for continuously and accurately monitoring the sweat glucose concentration.

Besides glucose, most electroactive molecules in sweat, such as uric acid (UA), ascorbic acid (AA), can be detected in neutral or weak acidic medium because of the easier deprotonation step. In this case, it is particularly important to optimize the working

potential by controlling the nanostructure and composite composition of functional materials to obtain precise response. Either carbon- or metal- based nanomaterials have been reported to quantitatively analyze such molecules. Wen's group developed a bi-functional wearable sensing system for simultaneously monitoring the UA and pH in sweat based on the chitosan/Au/laser-induced graphene (C-Au-LIG) modified sensor. Carbon- based electrode with high performance, low-cost, and good biocompatibility was a promising candidate for enzyme-free detection. Then, the Au electro deposition was performed in a commercial Au electroplating solution at  $-0.1$  mA for 10 s to further enhance the electron transfer rate. After that the appropriate chitosan solution was coated on the working area to create a super hydrophilic surface, remarkably improving the detection stability without damaging the porous structure of LIG. The resulting C-Au-LIG showed strong response current, which was almost twice that of LIG, and maintained the initial signal for more than one month in ambient environments. The C-Au-LIG based sensor was capable of detecting UA and pH, simultaneously, with high sensitivity and excellent selectivity. By the introduction of a microfluidic channel that could transport sweat to sensing area within 2 min the response currents of sweat UA and pH were recorded in real time and displayed on the mobile phone via the wireless communication.

#### *Non-electroactive molecules*

In wearable sensing field, the currently reported sweat components are mainly concentrated on glucose, lactate, AA and other electroactive molecules. Determination of non-electroactive metabolites and nutrients are rarely explored, as their structure or composition change is immune to the applied potential or current. Accordingly, MIP based sensor attracts ever-increasing attention due to the interesting natures of "artificial enzyme", such as good stability, high selectivity and low cost. Unlike the specific recognition of enzyme, antibody and aptamer, MIP sensor possesses selective molecular recognition sites by constructing the complementary cavities with the same size and shape as the biomarker in a polymeric network. The exposed cavities in polymer after removing Target templates exist interaction points that can combine with the biomarker closely.

### III. CHALLENGES AND FUTURE SCOPE

Wearable sweat sensor realizes real-time detection of the biomarker and rapid display of the result, regardless of space and time constraints, it has been a powerful tool to assist the early diagnosis and treatment of disease. The research of non-enzymatic sensor further facilitates the development of wearable sweat sensing, as it possesses the ultra-high sensitivity, outstanding stability and excellent long-term usage, avoiding the many restrictions of enzyme. However, in order to promote the comprehensive development of wearable non-enzymatic sensor in sweat detection, the following challenges urgently need to be addressed.

- 1) Although the sensitivity of non-enzymatic sensor is much higher than that of enzymatic sensor, it still needs to be further improved to enable trace analysis of some low-level sweat biomarkers, such as proteins, neuropeptides, and cytokines.
- 2) The selectivity of non-enzymatic sensor is unsatisfactory for detecting substances with similar structures.
- 3) With respect to glucose detection, many metal-based electro catalysts heavily rely on alkaline environment, which makes on-site and epidermal monitoring troublesome.
- 4) Multifunctional sensing array can be designed to simultaneously inspect environmental parameters of sweat (pH, temperature and ion concentration), so as to calibrate sensitivity to enhance accuracy. Detection of multiple target molecules together is conducive to make a more accurate diagnosis of the disease.

### IV. CONCLUSION

We have reviewed and highlighted the recent advances of wearable non-enzymatic electrochemical sensor toward the monitoring of sweat biomarkers. In terms of different detection systems (electroactive and non-electroactive molecules), sensing materials and electrolytes require to be changed accordingly.

Generally, either carbon-based materials or metal-based materials present the strong catalytic activity to electroactive molecules at the appropriate potential. However, till date, MIP sensor is the mainstream approach in the monitoring of non-electroactive sweat molecules. More enzyme-free sensing strategies are

urgently explored for such molecular detections. Integrating optical technology with electrochemical technology to detect sweat molecule is a good means, which cannot only expand the types of molecules detected at the same time, but also verify each other, thus improving the accuracy.

Overall, this review is of guiding significance for the design and development of wearable sweat sensor using non-enzymatic electrochemical strategy, striving to open a new era of medical equipment for personalized health management.

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