SWEAT ANALYSIS: A PAINLESS ALTERNATIVE TO REAL-TIME VITAL SIGNS ANALYSIS

PART 4: SYSTEM DESIGN

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The real-time analysis of sweat for the measurement of vital signs requires that sweat samples are evaluated as soon as they are produced. The sweat analysis system should also be made in such a way that adequate quantities of sweat can be collected before measurement. Given the physiology of sweat production, the system should also ensure that sweat samples will be produced even in the absence of sweat-stimulating triggers in the patient's surroundings. This section explains the design of a real-time sweat analysis system. Important features such as induction of sweating, sampling and sweat analysis are also provided.

Induction of Perspiration

Sweat differs from other biofluids that can be collected directly because its production is dependent on several physiological factors. Therefore, it is necessary to stimulate the body to produce sweat before this substance can be collected and analysed. Biological factors that promote perspiration and ensure the collection of specific quantities of sweat include aerobics and anxiety. In contrast, cold lowers perspiration. To generate sweat volumes that will be adequate for subsequent analyses, perspiration can be induced by modifying environmental factors such as relative humidity and temperature to tweak the body's regulatory systems, for example, the hormonal and sympathetic nervous system, or diet modifications. The administration of sweat-stimulating chemical compounds such as pilocarpine is also beneficial. The most reliable method of perspiration induction is the application of an electrical current of approximately 3.0 mA for about five minutes simultaneously with pilocarpine on a small area of the leg or arm.

Sampling of Sweat

A perfect sampler should be easy to use without posing any danger to the skin. It should also facilitate the quick collection of suitable quantities of sweat. The simplest sampling system in the studies considered here consisted of an occlusive patch made up of 2 to 3 sheets of gauze or filter paper. However, the major shortcomings of this approach were the inability to adjust the patches according to the patient's skin, skin irritation and alteration of the sample pH. Adopting the method was complicated by the necessarily large size of the patch that was required. A nonocclusive contrivance was adopted to circumvent the issue of skin irritation. Hooton and Li (2017) proposed the use of a patch made of Whatman filter paper attached to a surgical dressing sheet covered with a layer containing a bonding agent to facilitate the adjustment of the patch to the skin on the arm or leg. This patch permitted the selective conveyance of oxygen, water and carbon dioxide through the semipermeable film, enhancing the safety of the patch on the skin. The film also prevented the infiltration of non-volatile substances to the film.

However, the system permitted the vaporisation of water from concentrated sweat samples, thereby leaving behind only the solid constituents of sweat. Therefore, it was impossible to tell the total amount of sweat, which in turn affected the accuracy of the subsequent analyses in the identification of cystic fibrosis. Later, the use of sweat collection bags that precluded the free flow of water and air in and out helped to solve the problem of water evaporation. These bags were attached to the patch using adhesive rubber. The entire volume of collected sweat was retained in the bags. Thereafter, this design was enhanced by attaching pipettes, glass rollers and holders to facilitate the collection of sweat gathered in small quantities. This technology has been commercialised, and currently, Macroduct and Megaduct are readily

available commercial samplers (Luque de Castro, 2016). Furthermore, connecting sweat samplers with analytical instruments promotes efficiency.

Sweat Analysis

The efficacy of sample collection, as well as the accuracy and responsiveness of analytical techniques, can determine the excellence of sweat analysis. At present, several techniques can be used to test sweat that has not yet undergone metabolism. Nonetheless, a need to investigate drug metabolites in sweat remains. The principles that guide sweat analysers are colorimetry, conductivity, potentiometry and osmolality.

Colorimetry is an analytical technique applied in gauging the concentration of coloured substances. The method uses the Beer-Lambert law, which asserts that the concentration of a substance has a direct relationship with the quantity of light absorbed (measured as absorbance or optical density). The main instrument used for this purpose is a colorimeter, which comprises a sample cuvette, a source of light of varying wavelengths, a light sensor and a way of regulating the light source and interpreting the intensity of the transmitted light. Colorimetry has been applied in the creation of a microfluidic instrument for sweat analysis during fitness exercises in a regulated environment and long-distance bicycle contest in dry outdoor settings (Koh *et al*., 2016).

Conductivity is the degree to which an electric current, charge or heat can pass through a substance. Materials that allow electricity or heat to pass through them devoid of resistance are known as conductors. Two types of conductivity exist: thermal and hydraulic. Thermal conductivity is a measure of a substance's capacity to transmit heat, whereas hydraulic conductivity refers to the ability of absorbent materials to convey water. Conductance has been applied successfully in the diagnosis of cystic fibrosis (Liu *et al*., 2015; Mattar *et al*., 2014). In a

study performed by Mattar *et al*. (2014), cystic fibrosis diagnoses were eliminated in 714 out of 738 subjects using conductivity assays and chloride tests. The researchers also noted that conductivity values greater than 90 mmol/L corresponded to a sensitivity of 83.3% and 99.7% specificity and concluded that sweat conductivity tests provided high levels of diagnostic accuracy, matching those produced by sweat chloride. Therefore, sweat conductivity can be employed as an indicative exam for cystic fibrosis on its own.

Potentiometry is an analytical method used to determine the concentration of a substance in solution by measuring the electrical potential between two electrodes that have been immersed in a solution containing the substance under onvestigation. A high impedance voltmeter is useful for this purpose. Under static conditions, negligible current passes through an electrochemical cell. However, as the level of the electrolyte in the electrochemical cell changes, there is the flow of electrons from the solution to the electrodes following the application of a current. The degree of the electrical potential difference is related to the concentration of the electrolyte. This relationship can inform the deduction of analyte levels. Potentiometry has been applied in sweat analysis to determine physiological stress through the measurement of sodium ion concentration (Cazalé *et al*., 2016). This technique has also been employed in the development of a wearable chloride ion instrument (Choi *et al*., 2016).

Currently, different investigative methods have facilitated the analysis of drugs that can be excreted through sweat before undergoing metabolism. However, further investigations are needed to study drug metabolites that may be present in normalised sweat. Most sweat analysers employ the rules of colorimetry, potentiometry, osmolarity or conductivity. Capillary electrophoresis and chromatographic techniques – for example, liquid chromatography (LC) and gas chromatography (GC) – can be coupled with mass spectrometers (MS) to enable the precise

separation of compound metabolites or drug molecules in sweat (Jadoon *et al*., 2015). GC-MS linked to electron impact ionisation is commonly used for the study of drug content and concentration in sweat (Gentili *et al*., 2016). In addition, electrospray ionisation can be coupled to LC-MS/MS and used to determine drug levels in sweat. Other pertinent techniques include immunoassay methods such as radioimmunoassays and enzyme-linked immunosorbent assays. Overall, analytical techniques in sweat analysis are chosen based on the target analytes in sweat. Potentiometric ion-selective electrodes can be used for single moiety analysis, for example, sodium ions. Other alternatives for sodium analysis include sweat osmolarity analyser and the colorimetric chloride patch (Jadoon *et al*., 2015).

The variability of sweat sample volumes necessitates the normalisation of sweat volume to obtain reliable outcomes. Internal standards can be used to normalise sweat samples by measuring the quantities of sodium and potassium ions. However, it has been shown that measuring levels of sodium is a better method of normalising the sampled volume compared to estimation of potassium concentration (Jadoon *et al*., 2015).

A Prototype for a Wearable Sweat Analysis System

A typical sweat analysis system should have all three parameters explained previously: a means of sweat induction, a sampling system and an analytical system. However, for a wearable device that facilitates real-time analysis of sweat samples, additional constituents are necessary. The sensing constituent should be chosen based on the type of analysis involved. In any case, it should be made of flexible material with electrodes that are suitable for the target analytes to permit incessant multiplexed measurements. To improve the performance of the sensor, a supple polymeric shaft should encase the sensing electrodes to contain changes in pressure while forming a chamber for sweat collection. Such a design minimises sample losses by evaporation

and safeguards the skin from abrasion through direct contact with the skin. A printed circuit board (PCB) should also be attached to the sensor to aid in the calibration of unprocessed analyte signals into consequential concentrations and convey the data to a customised receiver, printout or phone application for easy read-outs.

Another alternative for signal transmittance is a radio frequency identification (RFID) chip customised for electrochemical detection of ions in sweat. In such an arrangement, sensing electrodes are attached to the same material as the wireless broadcasting constituent via electroplating, making it possible to shrink the entire setup into a wearable instrument. The RFID aerial conveys analyte readings to a smartphone for nonstop surveillance throughout the exercise period. Nevertheless, the efficiency of the sensor depends on near-field transmission between the patch constituents and smartphone to initiate sensing and data broadcasting. The patch also contains fundamental charge-storage modules to permit temporary, low-power procedures to carry on even if the distance between the smartphone and patch should temporarily increase beyond the recommended range. Overall, this system requires the smartphone to be held near the patch for optimal performance. Otherwise, the investigator risks disconnection and loss of data.

In cases where sweat monitoring is needed for clinical purposes, wearable sensors can be made to trigger local sweating via iontophoresis (Emaminejad *et al.*, 2017). The result is equilibrium sweat in inactive scenarios. In such a system, iontophoretic gadgets should have extra electrodes to apply local current in addition to the conventional pair of electrodes for sweat sensing. This extra set of electrodes is impregnated with a hydrogel that holds a sweat-stimulating drug that is taken under the skin by the flow of current. Sweat glands in the area surrounding the site of drug application are prompted to secrete sweat that can then be analysed to determine sweat analyte concentrations at equilibrium.

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