An Autonomous Diurnal Sweat Sampling Patch for Biomarker Data Analytics

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***Abstract*— Wearable sweat analysis possesses significant potential for transforming personalized and precision medicine, by capturing the longitudinal profiles of a broad spectrum of biomarker molecules that are informative of our body's dynamic chemistry. However, the lack of established physiological criteria to provide personalized feedback, based on sweat biomarker readings, has prevented the translation of wearable sweat-based bioanalytical technologies into health and wellness monitoring applications. Accordingly, scalable sweat sampling tools are required to facilitate large-scale and longitudinal clinical studies focusing on interpreting sweat biomarker readings. However, conventional sweat induction-collection tools are bulky and require multi-step and manual operations. Accordingly, here, we devise a sweat sampling patch, which can be deployed for autonomous diurnal sweat induction-collection. The core of this patch is an addressable array of miniaturized and coupled iontophoresis/microfluidic interfaces that can be activated on-demand or at scheduled time-points to induce/collect sufficient sweat samples for analysis. The iontophoresis interface was designed following an introduced design space centering on sufficient sweat secretory agonist delivery at safe current levels. The microfluidic interface was fabricated following a simple, rapid, and low-cost fabrication scheme. To achieve autonomous operation, these interfaces were extended into an array format and coupled with a custom-developed flexible and wireless circuit board. To inform utility, periodically induced/collected sweat samples of an individual were analyzed in relation to meal intake.**

***Index Terms*—Biomarker data analytics, health monitoring, iontophoresis, longitudinal sweat sampling, personalized and precision medicine, sweat analysis, wearable electronics.**

I. INTRODUCTION

TRACKING biomarker profiles provides insight into an individual's dynamically varying physiological status. To this end, sweat biomarker analysis platforms have emerged, which non-invasively capture the dynamic profile of a broad spectrum of molecules [1], [2]. However, the lack of established physiological criteria to contextualize sweat biomarker readings has inhibited the translation of such platforms into health and wellness monitoring applications. In that regard, scalable sweat sampling tools are required to facilitate longitudinal and large-scale clinical studies focusing on interpreting sweat biomarker readings with the aid of high throughput assays (*ex situ*) [1]. Commercially available sweat patches rely on passive perspiration (with low epidermal analyte flux), thus require biomarker accumulation over days [2]. Therefore, they fail to render the temporal resolution necessary to track the dynamic physiological processes. As an active sweat induction method with high epidermal analyte flux, iontophoresis uses an electrical current to deliver secretory agonist molecules to stimulate the sweat glands. In this way, by adjusting the applied electrical current, the agonist dosage and timing of the sweat secretion can be accurately controlled. However, the commercially available iontophoretic sweat induction (e.g., Macroduct and Nanoduct) and sampling tools are bulky, require large agonist-loaded hydrogel-skin area interfaces (> 3cm^2) and rely on multi-step and manual operations, inherently preventing their large-scale deployment for longitudinal studies. To realize a scalable sweat sampling tool suitable for large scale studies, we devised an autonomous sweat sampling patch, the core of which is an addressable array of miniaturized and coupled iontophoresis/microfluidic interfaces. In this implementation, each element of an array can be activated on-demand or at scheduled timepoints to induce/collect sufficient sweat samples for analysis. To achieve effective and safe sweat induction within a compact footprint, here, we particularly introduced a design space, to satisfy interdependent constraints imposed by sufficient agonist delivery and maintaining low increased skin temperature. To enable efficient routing and housing of µL-volumes of sweat, a thin film microfluidic module is fabricated, following a rapid, and low-cost fabrication scheme. The devised iontophoresis

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electrode arrays and the microfluidic module are vertically coupled with a programmable and flexible circuit board, forming a fully-autonomous and wearable sweat induction and collection patch. By tracking the sweat glucose levels of a subject throughout a day (specifically, pre/post meal intake), we illustrated the potential and significance of diurnal sweat sampling and analysis for clinical studies and personalized health monitoring applications.

II. Results and Discussion

A. System-level Design of The Sweat Sampling Patch

As shown in Fig. 1a, the autonomous sweat sampling patch is constructed by vertically integrating: 1) a flexible printed circuit board (FPCB) module with an on-board array of miniaturized iontophoretic electrodes, 2) an array of sweat secretory agonists-loaded hydrogels, and 3) an array of microfluidic sweat collection interfaces. These arrays are arranged radially to form a multi-compartment configuration. The iontophoresis interface of each compartment (e.g., C_1) can be activated at a desired time point (e.g., t_1) to deliver the agonist molecules with the aid of an electrical current underneath the skin to locally induce sweat secretion, where the amount of the delivered agonist can be controlled by adjusting the level and duration of the applied current (Fig. 1b). The secreted sweat is then collected into the corresponding microfluidic interface for further *ex situ* biomarker analysis. By programming the patch at the circuit level, this multi-compartment module can be adapted to autonomously take time-stamped sweat samples throughout the day (Fig. 1c).

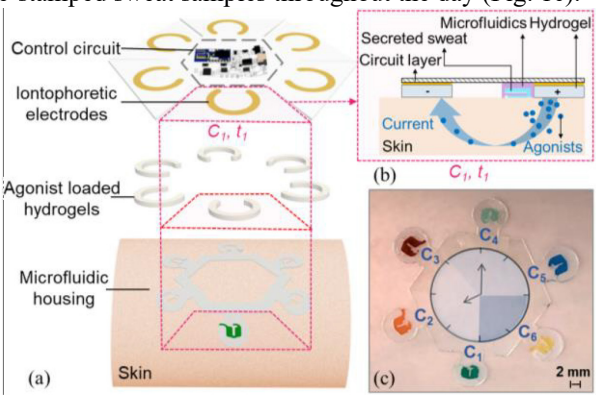

Fig. 1. (a) Exploded view of the sweat sampling patch, illustrating the vertical integration of a multi-compartment microfluidic housing, sweat secretory agonist-loaded hydrogels and a flexible circuit board with on-board iontophoresis electrodes (radially arranged positive terminals sharing a negative terminal at the center). (b) Illustration of agonist delivery underneath the skin with the aid of an electrical current for iontophoretic sweat induction (side-view). (c) Conceptual illustration of compartmentalized and time-stamped sweat samples, diurnally collected in the microfluidic module of the patch.

B. Iontophoresis: Design and Operational Parameters

Commercial iontophoresis interfaces (e.g., Macroduct and Nanoduct) rely on using relatively large electrodes [6] for sweat induction and sampling from the stimulated skin area, both of which are incompatible for the envisioned wearable applications. To miniaturize the iontophoresis interface, we need to consider the interdependent constraints: sufficient agonist delivery (proportional to the level and duration of the applied current) and maintaining the subsequently increased skin temperature (proportional to the duration of application and square of current density) within a safe operational range.

The amount of the agonist delivered (P, in mg), to the first order, can be estimated by the following equation:

$$P = \frac{I\,t\,M}{F} \qquad (1)$$

where I is in iontophoresis current in mA, t is the duration of iontophoresis application in seconds, M is the molecular weight of the agonist, and F is the Faraday constant (96489 C/mol).

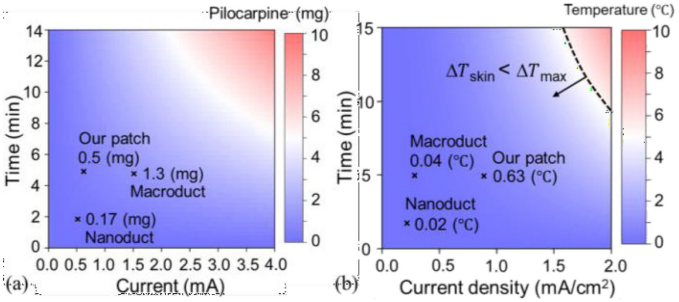

Fig. 2. (a) Estimated amount of the delivered pilocarpine for different iontophoresis current levels and durations. (b) Estimated increase in the skin temperature for different iontophoresis current density levels and durations. The dashed line indicates the conditions leading to maximum allowable temperature rise for the skin. The calculated dosages and skin temperature increments for our patch and two commercially available devices are annotated.

Following (1), and assuming pilocarpine as the agonist (systemic dosage: 10 mg [4], effectively setting an upper-bound) with 50% delivery efficiency [4], we calculated and plotted the amount of the delivered agonist molecules in Fig. 2a. Additionally, we estimated the increase in skin temperature (ΔT, Fig. 2b) by assuming that the electrical energy is dissipated as heat following the joule heating phenomenon, where $\Delta T \propto J^2\,t\,R$ (J: current density, R: skin resistivity) [3]. It is worth noting that the presence of hydrogel lowers the electrical resistance of the stratum corneum, which is particularly useful in reducing the ΔT [3], [5]. Based on these estimations, Macroduct (I = 1.5 mA, t= 5 min) and Nanoduct (I= 0.5 mA, t= 2 min) [6] interfaces deliver agonists on the order of 0.1-1 mg while the estimated skin temperature increase does not exceed the safety threshold (~6 °C [3]). As annotated in Fig. 2, for our iontophoresis interface, we selected operational parameters (I = 0.6 mA, t = 5 min) and electrode size (0.6 cm2), as an allowable operational point within the identified space, which ensures sufficient agonist delivery (~0.5 mg) with minimal temperature increase. Furthermore, to facilitate a lateral pathway for the stimulation of target sweat glands (that are the vertically below microfluidic interface, but laterally away from the induction interface), we used a ring-shaped iontophoresis configuration.

C. Circuit Design for Iontophoretic Actuation

As shown in Fig. 3, the circuit-level iontophoresis functionality is realized by employing a voltage-controlled current source, which allows for applying the desired current independent of reasonable variations in skin impedance. Our iontophoresis circuit features current limiting safety mechanisms at both the analog circuit (using a JFET-based current limiter stage) and software levels (real-time

monitoring/correcting with the aid of a bidirectional current shunt monitor stage). The desired iontophoresis current level and duration are set by programming the microcontroller unit, which can bidirectionally communicate with a custom-developed and Bluetooth-enabled mobile application.

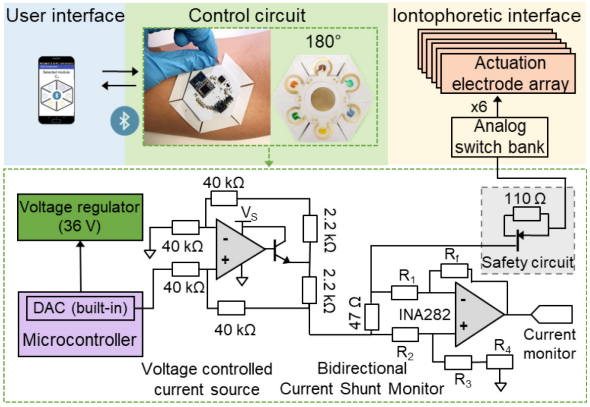

Fig. 3. Circuit diagram of the wirelessly controlled diurnal sweat sampling patch.

D. *Tape-based Microfluidic Module Fabrication Scheme*

As shown in Fig. 4, the microfluidic module is fabricated following a cost-effective and scalable microfluidic fabrication scheme [7] based on laser patterning and stacking double-sided tape (9474LE, 3M) and polyethylene terephthalate (PET, MG Chemicals) layers. The adhesive coating of the epidermal-facing layer and thinness of the complete flexible module altogether render a stable device-epidermal contact as well as efficient and microliter-level sweat sampling.

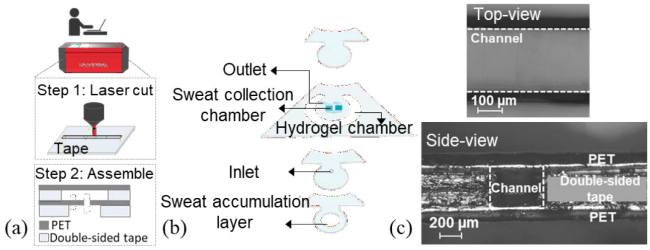

Fig. 4. (a) Fabrication procedure of the tape-based thin film microfluidic module. (b) Exploded view of the microfluidic module. (c) Optical microscope images of the side and top views of the tape-based microfluidic channel (two layers of PET sandwiching dual-layered laser-cut double-sided tape).

E. *Diurnal Sample Collection and Ex Situ Analysis*

By deploying our patch in a human subject study and following the established operational parameters, periodic sweat induction was performed at three designated time points during a day. Upon each induction, the secreted sweat sample was directly routed and collected within the microfluidic housing in the corresponding compartment. For each case, the sweat secretion profile was optically monitored (with the aid of blue-dyes embedded in the channel). The results indicated the complete filling of the designated sweat collection chambers following a relatively consistent secretion profile (within 30 minutes, Fig. 5a, b). Furthermore, to illustrate the utility of periodic iontophoretic sweat sampling for constructing the diurnal profile of biomarkers, six iontophoretically-induced sweat samples were collected from a subject before/after three main meals during a day. The collected sweat samples were then analyzed using our enzymatic glucose sensors (developed following our previously reported protocol [8]). As shown in Fig. 5c, the results indicated the elevations in sweat glucose level upon food intake.

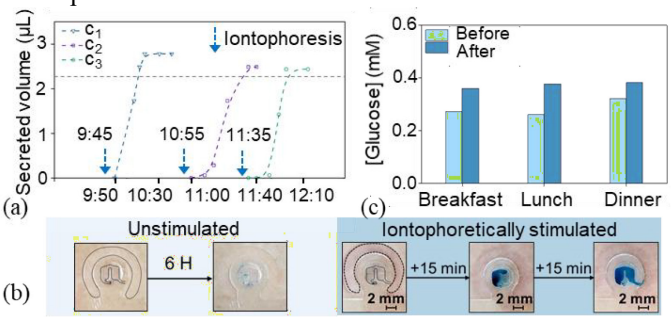

Fig. 5. (a) The induced sweat secretion profiles by three representative compartments in our patch at three timepoints. Arrows mark the iontophoresis initiation (for 5 min stimulation). The dotted line marks the minimum sweat volume for biomarker analysis. (b) Unstimulated and iontophoretically-stimulated sweat collection into a microfluidic chamber (placed on a subject's forearm). The dotted lines depict the perimeter of the hydrogel-skin interface and the collection chamber (c) Sweat glucose levels of a subject before and after the three main meals. Agonist-loaded hydrogel used: 0.5% pilocarpine nitrate (PILOGEL®, reshaped to match the iontophoresis electrode footprint).

III. Conclusion

Informed by an introduced design methodology and following a low-cost microfluidic device fabrication/system integration scheme, we developed an iontophoretic sweat sampling patch. This patch can be deployed in large-scale and longitudinal clinical studies to autonomously collect time-stamped sweat samples. By analyzing these sweat samples with high throughput assays, large contextualized biomarker datasets can be created. These datasets can be coupled with advanced data analytic algorithms to establish criteria for providing actionable feedback based on sweat biomarker readings. In this way, the presented technology catalyzes the translation of wearable sweat-based bioanalytical technologies into health and wellness monitoring applications.

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