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Pre Symptomatic COVID Screening

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Abstract

Temperature checks for fever are extensively used for preliminary COVID screenings but are ineffective during the incubation stage of infection when a person is asymptotic. Researchers at the European Centre for Disease Prevention and Control concluded that approximately 75% of passengers infected with COVID-19 and traveling from affected Chinese cities would not be detected by early screening.

Core body temperature is normally kept within a narrow range and has the smallest relative standard deviation of all vital signs. Heat in the body is prioritized around internal organs at the expense of the periphery by controlling blood flow. In fact, blood flow to the skin may vary by a factor of 100 depending on thermal conditions. This adaptation causes rapid temperature fluctuations in different skin regions from changes in cardiac output, metabolism, and likely cytokine diffusion during inflammation that would not be seen in average core body temperature. Current IR and thermal scanners used for temperature checks are not necessarily reflective of core body temperatures and require cautious interpretation as they frequently result in false positive and false negative diagnosis. Hand held thermometers measure average skin temperatures and can get readings that differ from core body temperature by as much as 7°. Rather than focusing on a core body temperature threshold assessment we believe that variability of temperature patterns using a novel wearable transdermal microneedle sensor will be more sensitive to infections in the incubation stage and propose to develop a wearable transdermal temperature sensor using established Sandia microneedle technology for pre symptomatic COVID screening that can additionally be used to monitor disease progression at later stages.

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1. Introduction

Widespread implementation of COVID-19 testing using standard detection devices is limited by cost, size, and complexity which typically require the collection of specimens from the patient and transfer to device at a laboratory for analysis. Wearable point of care diagnostic devices are emerging as valuable tools for individual health monitoring and have potential to enable rapid and early detection of viral infections and monitoring severity as the disease progresses. However, current wearable technologies mainly provide health data based on vital signs that are difficult to interpret for accurate detection of infection. Microneedle sensors have been exploited for measuring circulating biomarkers in the dermis due to their ability to puncture the skin's stratum corneum and access interstitial fluid without irritating deeper layers of the skin associated with pain, blood flow, or sensation. This allows minimally invasive measurement of host response biomarkers for the development of wearable point of care diagnostic monitoring to detect viral infections such as COVID-19.

Diagnosis using vital signs stand alone is not particularly effective, especially when based only on the magnitude of absolute values, However there is a growing body of evidence that the trends and variabilities from combinations of vital signs can be used to predict sepsis, outcomes of critically ill patents and correlated to specific disease states. Uncharacteristic changes in core body temperature were observed during the incubation stage of viral and bacterial infections and in critically ill patients with gram negative bacterium that preceded fever. Abnormal temperature patterns with an increase in magnitude and oscillatory frequency over 24-hour periods were recorded for up to 3 days before any obvious signs of infection in septic patients. This indicates that temperature patterns if measured continuously could be used for pre symptomatic screening of infection.

The skin has a primary role in thermoregulation and has a physiologically unique microvasculature where its circulatory capacity far exceeds its metabolic needs. not seen in any other organ in the body. Blood flow to the skin may vary by a factor of 100 depending on thermal conditions. This adaptation causes rapid temperature fluctuations in different skin regions from changes in cardiac output, metabolism, and likely cytokine diffusion during inflammation. We have developed a proof of concept microneedle diagnostic device to measure temperature in the skin. The signature patterns from temperature variations which are characteristic of inflammation can be used for the

detection of COVID at pre-symptomatic stage and can additionally be used to monitor disease progression at later stages.

Our previously developed microneedle arrays were converted into a temperature sensor using fine wire gauge thermocouples that can easily be inserted into the needle bores and were calibrated ex vitro. We have also done modelling to measure the effect of probe on transient heat conduction. Transdermal temperature monitoring has implications for other applications such as sepsis, diabetes, organophosphate detection, performance and disease states in general which would be of interest for agencies such as DTRA, DARPA and NIH.

Results

A detailed representation of the upper layers of the skin, including multiple layers of blood vessels and capillary loops, were used to create a computational model using Sandia's Sierra finite element modelling code suite to model heat transport within the layers providing details reference to the body conditions that the microneedle-based sensors will observe. The computational model in Figure 1 combines blood flow through the complex vessel/capillary networks and the associated heat diffusion and convection. By parametrizing the geometry, the model can quantify the impact of vasodilation/constriction on heat transport to the skin surface through vessels, a key mechanism for thermoregulation of the body.

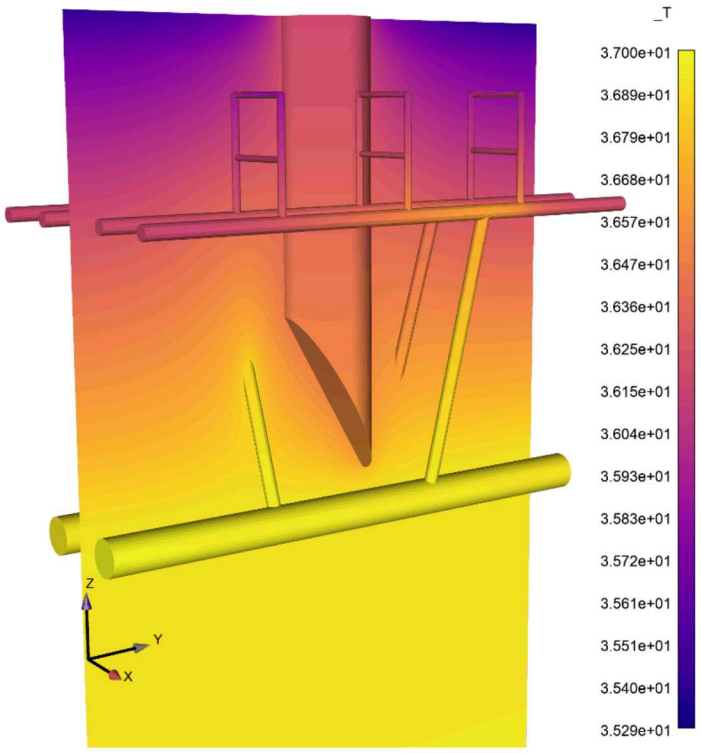

Figure 1: Parameterized geometric representation of the upper layers of skin, including blood vessels and capillary loops. The nearest vessel shows vectors representing blood flow rates through the vessel. Vessel walls colored by blood pressure. Slices through the entire domain indicate the local temperature, showing that capillary loops provide the primary heat transport to the skin surface.

Temperature sensing microneedles were explored using COTS thermocouple wires due to their availability and known performance. Two K-type thermocouple wire diameters (25um and 50um) were selected in order to fit within the range of generally accepted microneedles sizes being less than 500 μm in diameter and around 1000 μm in height. Wires were bonded using a thermocouple bonder and cleaned using ethanol, DI water, and nitrogen stream. The wires were first insulated by coating 3μm of parylene C and then cut at the distal end leaving only the circular distal end the primary heat conduction pathway. Several depositions were used to validate the adhesion strength of the deposited coating until delamination was not seen without physical abrasion. Threading of the thermocouple into stainless steel microneedles was performed by tightly twisting the microneedles by hand and using a microscope to align the bore with the wires. Since the bonded end of the needles ranged in size, needles were threaded from the terminal side through the tip and glued in place once the thermocouple junction location was determined. Initial testing showed that threading the 25um K-type wires into 32 Gauge needles was possible but quite challenging. Our yield for this project was 2 of 7. Images of thermocouple threading into needle bores before and after insertion are shown in Figure 2 A and B respectively. 50um K-type thermocouple wires inserted into the 25G gauge needles were the final configuration chosen. Issues of thermocouple damage due to threading was not seen with needle/wire gauge (n=4). Larger gauge needles, with smaller outer diameter, would be compatible with the 50um K-type wires, but were not tested during this project. Insertion tests were performed in tomato plants to validate how well the needle-thermocouple assembly could withstand insertion. This assembly withstood 5 insertions and in-situ temperatures measurements into tomato stems recorded that the peripheral temperature to be ~2C below RT. Further studies can now begin in vivo validation using human subjects at Sandia Medical after modification of already approved Human Studies IRB protocols in place for microneedles

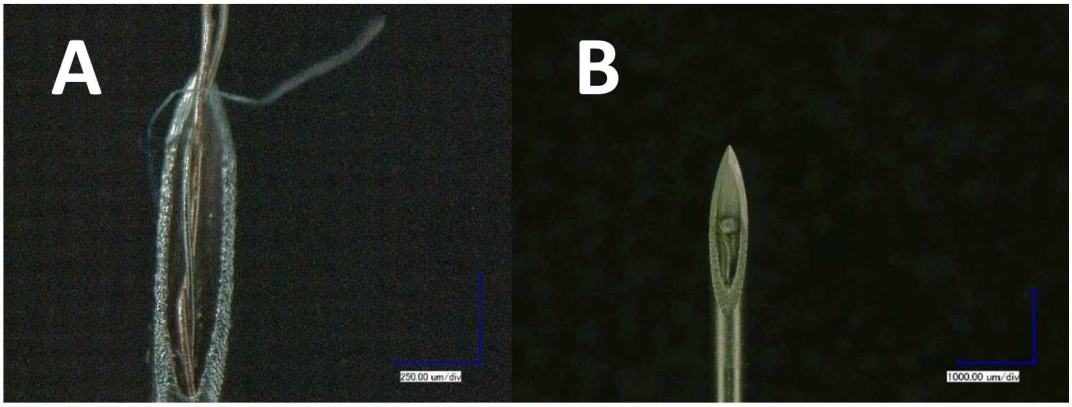

Figure 2: Threading of the thermocouple into stainless steel microneedles (A) before assembly and (B) after

In summary, Sandia's Sierra finite element modelling code suite was used to code heat transport within the skin layers providing details reference to the body conditions that the microneedle-based sensors will observe. The computational model accounts for heat diffusion and convection and blood flow through the vessel/capillary networks. The parametrization of the geometry allows the model to quantify the impact of vasodilation/constriction on heat transport to the skin surface through vessels to guide the microneedle temperature sensor development.

Temperature sensing microneedles were also developed using Sandia microneedle arrays and compared against two K-type thermocouple wire diameters (25um and 50um). Preliminary testing in a plant surrogate for validation. This work provides the basis for future development of a minimally-invasive wearable continuous temperature monitor to longitudinally monitor trends in temperature patterns in the dermis. We believe that the advantages of a dermal temperature monitoring over external non-invasive skin temperature measurements, such a IR, devices is that temperature monitoring from precise microneedle placement of the probe into the dermis microenvironment between vessels and the epidermis will be more sensitive to small and rapid fluctuations in skin temperatures to better inform on health states. The device can be adapted to include additional vital sign measurement capabilities such as heart rate and pulse and when combined with other biomarker data streams functions as a powerful new approach for disease assessment based on signature patterns

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