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Development of a compact fluorescence spectroscopy sensor for non-invasive monitoring gut function

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Abstract: Monitoring gut permeability is currently either invasive, inaccurate or difficult to perform in infants. We present a compact fluorescence sensor that overcomes some of these limitations, paving the way for non-invasive gut permeability monitoring.

1. Introduction

Changes in intestinal function, particularly gut permeability, are associated with a range of health disorders including inflammatory bowel disease, coeliac disease and malnutrition [1,2]. However, current techniques for assessment of gut permeability (e.g. endoscopic biopsy and histopathology, Lactuse:Mannitol (L:M) tests, etc.) are either highly invasive, unable to provide complete diagnoses and/or difficult to perform in infants [3]. Moreover, the mechanism and interactions behind the role of the gut in the above conditions (and others) are not well understood. As such, improved diagnostic tools that provide non-invasive and reliable measurement of gut permeability (and other elements of gut function) could have significant clinical benefits [4,5].

Transcutaneous fluorescence spectroscopy has recently been proposed for this purpose, where subjects consume an oral dose of a fluorescent contrast agent and a non-invasive probe detects the fluorescence signal at the skin as the dye permeates from the gut into the blood stream [6-9]. Proof-of-concept results have been reported that demonstrate that transcutaneous spectroscopy of orally ingested fluorescein – a clinically approved fluorescent contrast agent – has potential for non-invasive monitoring of gut permeability and other gastrointestinal functions in the clinic [7-9]. However, to date, this technique has only been deployed using laser-based benchtop or trolley-mounted spectrometers, which are both large and expensive [6,7,9].

2. Towards compact, wearable transcutaneous fluorescence sensors

To allow more widespread clinical deployment of transcutaneous spectroscopy, here we present a compact fluorescence sensor for gut permeability monitoring. The key function of the device is to detect fluorescence signals at the skin as an orally ingested contrast agent (typically fluorescein) permeates through the gut barrier into the blood stream. The sensor employs one light emitting diode (LED; 465nm peak intensity), two Silicone PIN photodiodes (PDs; 70% relative spectral sensitivity at 500 nm) and three flexible reflective optical filters (cut-off wavelength at 500nm; two short pass, one long pass filter). Custom-made electronics and 3D print designs were developed to amplify the signal, reduce background light and assemble/mount the optical components (Fig. 1).

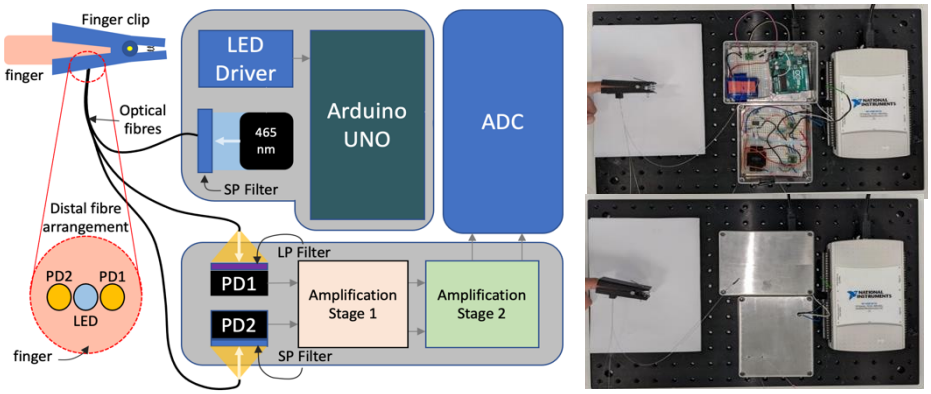

Fig. 1. (*left)* Diagram of the compact fluorescence sensor (2nd prototype). *(right)* Photographs of the 2nd prototype sensor with electronics containers in open (top) and closed (bottom) configurations. Optical fibres deliver light from the sensor (LED and PDs) to the 3D printed encapsulation attached to the participant's finger.

In the first iteration of the sensor the LED was placed between the PDs, maintaining the same interrogated area for both PDs. Due to physical limitations of the electronics, the minimum achievable PD-LED spacing was 2.8 mm. Both PDs and LED were then placed in contact with the skin. The performance of this first prototype was tested on different concentrations of fluorescein diluted in water (concentration range: 0.0017–0.02 mg fluorescein per ml water). At the same time, an Ocean Insight

spectrometer (FLAME-S-VIS-NIR-ES) was used to collect spectra for each concentration (with illumination provided by a 488 nm laser source). There is correlation between both datasets, Fig. 2(*left)*, showing that an increase in fluorescein concentration leads to increases in both sensor output voltages and spectral peak intensity values. However, tests performed in a human volunteer demonstrated that the sensor was not sensitive enough to detect fluorescein in the blood stream (with the sensor placed at the fingertip) following oral ingestion of the dye. This was attributed to the 2.8 mm spacing between the PDs and the LED, which was greater than the source-detector spacing used in previously reported laser-based systems (e.g. [7,9]).

As such, a second prototype sensor (see Fig. 1) was developed in which we increased the PD amplification and, more importantly, reduced the distance between the light source and detectors at the skin. To accomplish the latter improvement, light was transported to the tissue and back to the PDs through optical fibers (with custom 3D printed mounts used to mount the fibers at the fingertip). This device was tested on fluorescein solutions with concentrations (0–1.7 µg fluorescein per ml water) chosen to approximate the expected signal levels at the fingertip following oral ingestion of fluorescein. The data was compared against that collected with the first prototype sensor and the Ocean Insight spectrometer. Fig. 2(*right*) shows the results obtained from the second prototype sensor alongside the peak spectral intensity values at the respective concentrations. As shown in Fig. 2(*right*), output voltage values from the second prototype qualitatively correlate with peak spectral intensity values for each concentration.

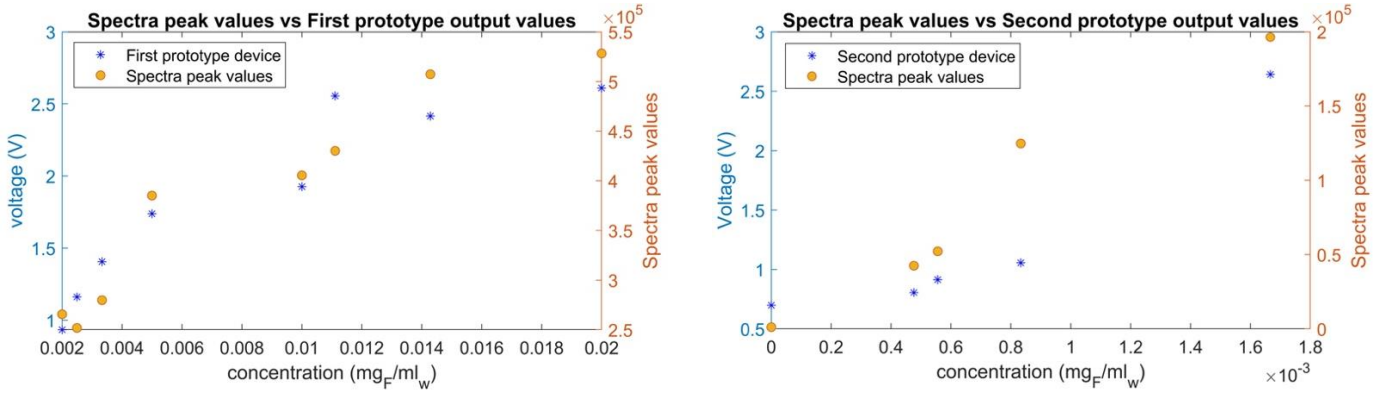

Fig. 2. Sensor output voltages (blue asterisks) and spectral peak intensities (orange circles) as functions of fluorescein concentration. (*left*) 1st prototype – concentration range: 0.0017–0.1 mg fluorescein per ml water. *(right)* 2nd prototype – concentration range: 0–1.7 µg fluorescein per ml water.

To demonstrate the performance of the second prototype device in a real scenario, we are now deploying the sensor in a clinical trial to measure fluorescence signals at the fingertip in participants who ingest 500 mg fluorescein dissolved in 100ml water (with signals compared to data collected at the same time using the trolley-mounted spectrometer reported in [7]). In an initial test, the data collected with the miniaturised sensor correlated well with data from the larger and more expensive trolley-mounted system, demonstrating the potential of the device for non-invasive monitoring of gut permeability (data to be presented at conference).

3. Conclusions

We have developed and tested a portable fluorescence spectroscopy sensor for non-invasive monitoring of gut permeability. The sensor uses an LED and two PDs for excitation and detection of fluorescence, along with optical fibres to deliver light to and from tissue while also minimizing separation between light source and detectors. Preliminary results demonstrate the capability to detect fluorescein *in vivo* following oral ingestion, indicating the potential for clinical monitoring of gut permeability in the future.

4. Disclosures

A.J.T. is author of a patent regarding the use of transcutaneous spectroscopy for non-invasive assessment of gut function.

5. References

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