Point-of-care, continuous assessment of multiple biomarkers using long wavelength near infrared spectroscopy for dialysis

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Summary of abstract -
Dialysis is a crucial treatment for chronic kidney disease (CKD). In this routine treatment quality care can be ensured by continuous, nondestructive monitoring to avoid clinical complications like sepsis. Long wavelength near-infrared (LWNIR) spectroscopy shows promise in providing continuous, point-of-care monitoring. This paper demonstrates the application of LWNIR spectroscopy for measuring multiple biomarkers—specifically lactate and urea— in a microfluidic system simulating a channel for dialysis. The spectroscopy calibration is based on liquid phantoms containing various interfering biomolecules.
Technical abstract –
Chronic kidney disease is treated with routine dialysis. Routine dialysis benefits from continuous monitoring of key biomarkers like lactate and urea in its effectiveness and early warning of complications like sepsis in patients. Current standard of care includes laboratory measurements using a sample. Long wavelength near-infrared (LWNIR) spectroscopy could potentially provide the optimal solution for non-destructive, continuous and point-of-care monitoring in peritoneal dialysis systems. However, LWNIR spectroscopy suffers today from poor calibration and specificity because of spectrally interfering biomolecules. In this work, we develop a novel method of calibrating machine learning algorithm with liquid biophantoms, in place of multiple patient samples to provide wide variability due of selected spectrally interfering molecules. Using this liquid biophantoms model we see two distinct sets of wavelengths that are relevant to determining biomarker concentration with and without the interferers. The model trained with the high variability liquid biophantoms is used to determine biomarker levels spiked serum in a microfluidic system simulating a channel for dialysis.
Keywords: long wavelength near infrared spectroscopy, hypoxia, dialysis, sepsis, transmission spectroscopy, machine learning

1. INTRODUCTION

Chronic kidney disease (CKD) is a condition where the kidneys do not function properly due to damage. Although CKD has no cure, treatments in advanced stages can help alleviate symptoms. Dialysis is one such treatment used by approximately 4 million people worldwide. It replicates some of the kidney's functions by diverting blood to a machine that removes waste products and excess fluid [1]. Approximately 11% of dialysis procedures are peritoneal dialysis, where the lining of the abdomen (peritoneum) acts as a filter instead of the kidneys. This type of dialysis can be easily performed at home daily.

Lactate, along with urea, is one of the key biomarkers in peritoneal dialysis. As of today, liquid chromatography and other laboratory-based methods are used to determine the quality of dialysis by taking a sample before and after dialysis. It not only indicates the progress of dialysis but also helps monitor complications such as sepsis [2-5]. Long wavelength near-infrared spectroscopy (LWNIRS) in the range of 1400-2500 nm offers an effective solution for continuous, non-destructive measurement of biomarkers related to CKD [5,6]. However, a major challenge in accurately assessing biomarker concentrations is the interference from other biomolecules [7-9]. Current predictive machine learning models rely on measurements from healthy patients to form the training data set. However, the healthy patients dataset does not span all the physiological ranges of the biomolecules seen in patients in clinical situation.

In this paper, we develop a novel liquid biophantoms training set with a subset of biomolecules present in serum such as lactate, urea, albumin and glucose. These biomolecules are chosen as they spectrally interfere with each other in LWNIR wavelengths and have significant concentrations in serum. In the liquid biophantoms, the biomolecule’s concentrations span beyond the healthy clinical levels to the complete physiological range. This approach helps identify the relevant wavelengths for monitoring two key biomarkers in dialysis: lactate and urea. The LWNIR spectroscopy spectra of these biophantoms are captured and form the basis for wavelength selection. We demonstrate the effectiveness of these wavelengths in a simulated dialysis system using serum.

2. METHODS AND MATERIALS

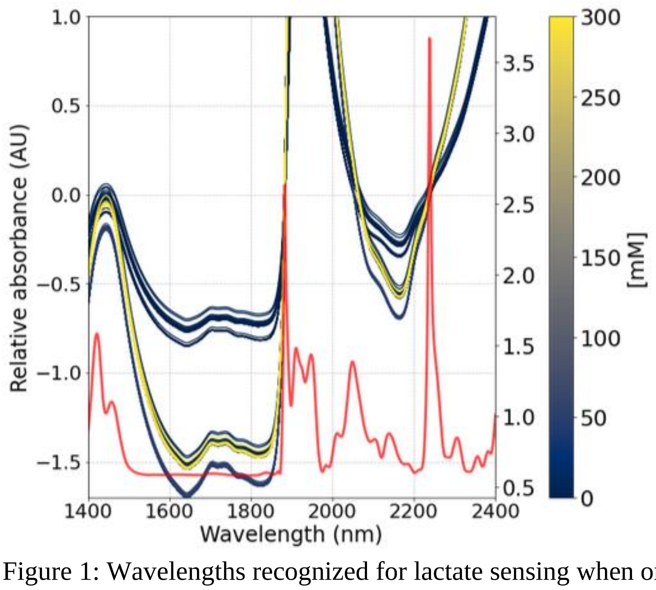
The optical system was based on a custom transmission system with an LW-NIR source (Lamp with 2400 K – ILT L8008) fiber coupled to a collimator to produce 2 mm Ø beam. The sample was illuminated by the source in a 0.5 mm thick quartz cuvette (Hellma Z804541). The transmitted light was collected into a low-OH optical fiber (Thorlabs M47L01) using a collimator and measured on a LW-NIR spectrometer (Hamamatsu C15511-01 FTIR-Engine) capable of measuring between 1100-2500 nm [9]. A microfluidic system simulating a channel for dialysis was developed using a peristaltic pump. The pump was used to flow serum through the cuvette and the level of lactate or urea was changed at different time points during measurement.

The liquid biophantoms were prepared in phosphate buffer solution (PBS) and other biomarkers were lactate (Fisher S/5161/08), glucose (Sigma G8270, 0-740 mM), urea (Sigma 1084880250, 0-740 mM), and albumin (Sigma A1653, 0-187 mM). For each level of lactate nine solutions with low, medium or high levels of interfering biomolecules glucose and urea were prepared with albumin remaining constant. Similarly, urea was measured with interference from glucose and lactate. For each sample 70 spectra were collected.

A machine learning algorithm based on partial least square regression was used for data analysis and model development [10,11]. The measured absorbance spectra, consisting of 10000 wavelength points was normalized to PBS spectrum. Normalized spectra were smoothed using Savitzky-Golay filter of 51point window and a third order polynomial. A standardization scaler was applied before partial least square regression model. A 5-fold cross-validation was performed to determine the latent variables. Variable importance in projection (VIP) is calculated which is used as a measure of the importance of the wavelength in predicting lactate biomarker's concentration. VIP>1 are important for the model.

Optical spectrum in the pump model was recorded and used as test against the developed liquid biophantoms model to determine the biomarker levels.

3. RESULTS



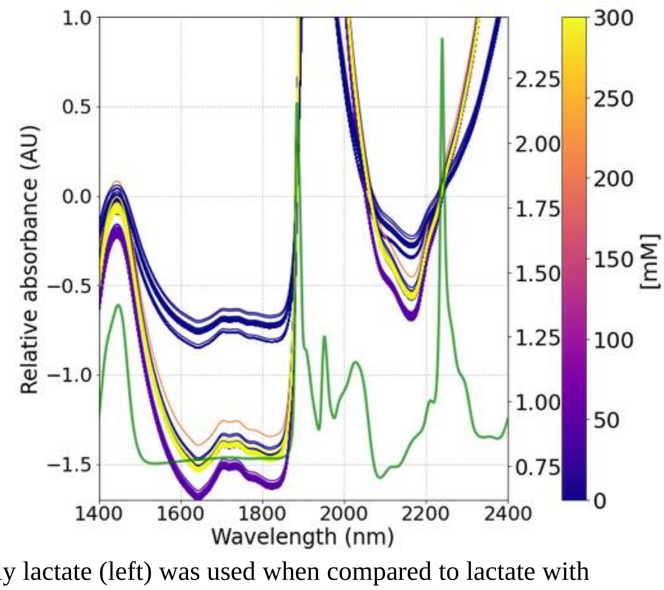


Figure 1: Wavelengths recognized for lactate sensing when only lactate (left) was used when compared to lactate with interferers was used (right) are different.

Relative absorbance to the buffer solution was plotted for liquid biophantoms for varying lactate levels (shown in colormap) with the plot on left without interfering biomolecules and right with interferers for lactate as shown in **Figure 1**. The VIP score of each wavelength is plotted in the red or green line plots on the spectra. The wavelengths with VIP score > 1 can be considered as relevant for estimating the lactate levels. While a subset of wavelengths remains consistent across the phantoms, some regions clearly differ between the two.

4. CONCLUSIONS AND FUTURE WORK

Our system was capable of measuring the different levels of biomarkers in liquid biophantoms with other interfering biomolecules Machine learning algorithms calibrated using these biophantoms will be to determine the levels of biomarkers in a microfluidic system simulating a channel for dialysis.

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