A miniaturized ball-lensed fiber optic NIR transmission spectroscopy-based glucose sensor

Silje S. Fuglerud, Karolina Milenko, Ine L. Jernelv, Astrid Aksnes, Reinold Ellingsen, Dag Roar Hjelme

Department of Electronic Systems, Norwegian University of Science and Technology, Trondheim NO-7491, Norway

silje.fuglerud@ntnu.no

Abstract: A novel ball-lensed fiber transmission sensor is presented aimed at *in vivo* continuous glucose monitoring of diabetics. Preliminary results yield 20 mM RMSE, limited by mechanical instability. The design enables flexibility and further miniaturization.

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1. Introduction

Vast research is being conducted on a variety of glucose sensing devices in pursuit of more effective treatments for diabetes mellitus (type 1). The goal is to enable continuous glucose monitoring and improved treatment to avoid harmful effects of either too high (hyperglycemia) or too low (hypoglycemia) blood sugar levels. The state-of-the-art of continuous glucose measurements are subcutaneous measurements, where an electrochemical sensor is placed in the interstitial fluid. These sensors have good selectivity but suffer from limited lifetime and the need for frequent calibration by inconvenient fingerprick tests. As an alternative, optical glucose sensing could provide a long-term option for continuous glucose measurements.

The research on glucose sensors using wavelengths in the near infrared (NIR) has focused largely on non-invasive sensors to be placed on the skin. The technique held great promise, but has proved difficult to calibrate across individual and situation dependent changes in the skin scattering. Several groups have aimed at using new and advanced techniques to measure glucose, for example by implantable waveguides [1] or microdialysis into a microfluidic chip [2]. Although novel, these techniques still require further development. Here, we re-investigate a well known system: spectroscopic transmission measurements. To adapt the system to *in vivo* use, we replace the traditional cuvette with ball-lensed fibers. A somewhat similar approach has been previously suggested [3], using a ball lens reflection probe with a large core optical fiber in a non-invasive rat study. A ball-lens sensor based on a single mode (SM) fiber with a mirror has also been applied *in vitro* to aqueous glucose [4], but only using the peak power corresponding to one wavelength channel. Beyond these studies ball-lensed fibers do not appear well explored for glucose monitoring.

2. Experimental procedure and results

Standard SM fibers for 1260 nm to 1625 nm with 8 µm core and 125 µm diameter were used. The SM fibers were chosen to avoid mode interfering noise. The ball-lenses were created using a FSM-100P ARCMaster by Fujikura. The ball-lensed fibers were aligned in a v-groove and fixed with two-component water resistant epoxy resin. The distance between the tip of the ball lenses were aligned at 3 mm to fit the optimal path length of the first overtone, where glucose has absorption features around 1600 nm to 1700 nm.

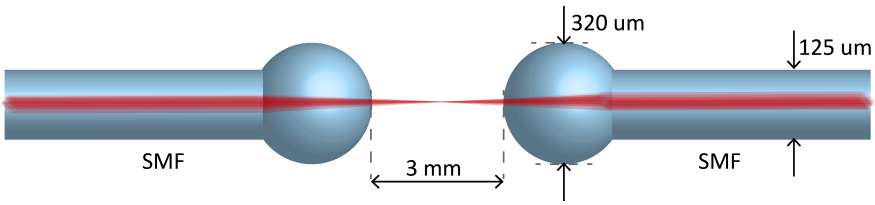

Fig. 1: The glued ball lenses with a spacing of 3 mm. The ball lenses were approximately 320 µm in diameter.

The fibers were connected to a white-light laser and a NIRQuest512 spectrometer. The output power after the transmission measurements was approximately 1 mW. A series of measurements were conducted with glucose concentrations 100 mM, 200 mM, 300 mM, 400 mM and 500 mM. The fibers and the groove were flushed with destilled water and ethanol between each measurement and excess fluid was absorbed. The background spectra in water were measured before each glucose measurement. The spectra were collected with 200 ms integration time and averaged over 20 scans.

To remove noise effects, a third order Savitzky-Golay filter was applied. The absorbance was found by Beer-Lambert's law: $A = -\log(I/I_0)$, with I_0 being the preceding water spectrum.

A regression model was found using a partial least squares regression (PLSR) algorithm. The strong and noisy pump signal around 1064 nm was downweighted by 0.2. Wavelengths below 1300 nm were downweighted by 0.5, as the fiber is not SM below 1260 nm and displayed interfering modes. Eight measurements were used for calibration, with leave-one-out cross-validation. A root mean square error (RMSE) of calibration of 20 mM and a corresponding RMSE of prediction of 28 mM was achieved with a two-component regression model.

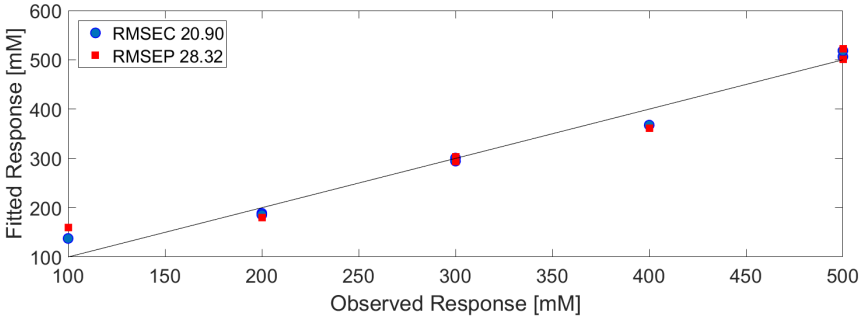

Fig. 2: The resulting two-component regression model from the PLSR, explaining 96.7 % of the variance.

3. Discussion and conclusion

This paper presents preliminary results and is considered a proof of concept. The sensitivity must be increased considerably to be of use *in vivo*. The high variability of the signal is largely due to mechanical shifts during cleaning causing alignment shifts. This will be addressed and the setup will be improved further for stability, robustness and miniaturization.

Intensity measurements are prone to changes in the surrounding environment between scans, and the authors will also work towards identifying reference-wavelengths that can be used for signal correction. Other chemometric methods such as extended multiplicative scattering correction (EMSC) can also improve the calibration.

Ultimately, the system is intended for *in vivo* online monitoring. To achieve this, we need to go beyond the traditional measurement series producing one regression model. The work presented consists of standard components but combined into a more flexible and movable sensor where the algorithms can be tailored for *in vivo* applications. Although the sensitivity should be improved, the initial results show great potential towards the goal of creating a reagent free glucose sensor.

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