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Towards Remote Fiber-Based *In Vivo* Sensing of Glucose by Near Infrared Spectroscopy

Silje Skeide Fuglerud[1,2,*] **and Dag Roar Hjelme**[1]

[1] *Department of Electronic Systems, Norwegian University of Science and Technology, Trondheim, Norway*
[2] *Department of Endocrinology, St. Olavs University Hospital, Trondheim, Norway*
[*] *silje.fuglerud@ntnu.no*

Abstract: A stable and low-noise system is required to measure small changes in biochemical constituents such as glucose. We discuss the requirements and limitations to achieve the necessary stability using a supercontinuum source. © 2021 The Author(s)

1. Introduction

Diabetes mellitus 1 is a disease that requires continuous measurements of the blood glucose levels to provide accurate treatment. Too high glucose levels (hyperglycemia) can cause health problems over time, such as diabetic foot or blindness, and a decrease in general health. Too low glucose levels (hypoglycemia) are dangerous in the short term, and can lead to acute symptoms and even death. The state of the art for continuous glucose monitoring (GGM) devices are electrochemical sensors that are placed in the interstitial fluid in the skin. However, these must be replaced as often as every one-two week, and the accuracy of the sensor may suffer from inflammatory responses in the sensor injection site. These sensors are not reliable enough to base fully automatic insulin administration on the measurements. Optical glucose sensing could be an alternative that does not need to be exchanged as often. More specifically, spectroscopy at near infrared (NIR) wavelengths can be a feasible approach, as there is already a plethora of sources, detectors and optical fibers close to telecommunication wavelengths. Accurate NIR spectroscopy could also be used to monitor other biomolecules, such as urea and lactate [1]. Most broadband sources used for NIR spectroscopy suffer from low spectral brightness, potentially limiting performance. The compact supercontinuum sources with high spectral densities have not yet been widely adopted for absorption spectroscopy due to the relatively high amplitude noise levels [2, 3]. Herein, we discuss the limitations and possible solutions to achieve the accuracy needed for an optical fiber-based system with a supercontinuum source at NIR wavelengths, for aqueous glucose measurements.

2. System configurations

We have previously estimated that a spectroscopy system to measure glucose in the NIR range must be stable enough to detect changes within 0.03 %, which sets a bound on the coefficient of variation (CV) ($\mathrm{CV} = \sigma_f / f$, where f is the signal and σ_f is the standard variation) [3]. The source power must overcome the photocurrent and thermal noise variance of the detector. In [3], a broadband source had too low power to fulfill this for an extended InGaAs spectrometer. The supercontinuum sources that were investigated had an adequate brightness, but too high relative intensity noise (RIN) to be employed directly. The setup was therefore modified with a reference arm and the spectrometer was substituted with an acousto optic tunable filter (AOTF) (SuperK Select, NKT Photonics, Denmark) for wavelength selection ($\Delta\lambda = 6.4$–19.8 nm) combined with single detectors (DET01, Thorlabs, US) to relate the RIN of each pulse ($\tau \approx 2$ ns) from a supercontinuum laser (SuperK Compact, NKT Photonics).

The setup in [3] was limited by characterization noise from the 8 bit analog to digital converter (ADC). Possible options to improve the digitization of the signal were a fast digitizer, a boxcar integrator or a lock-in amplifier. Based on cost and performance, a 14 bit ADC digitizer card (M4i4450-x8, Spectrum Instrumentation, Germany) with 500 MS/s and a bandwidth up to 250 MHz was chosen. Although the reduction in bandwidth of the original pulse reduces the signal strength, lower bandwidth will also average the high-frequency noise. A maximum signal to noise ratio (SNR) for a 2 ns pulse has been estimated to 50–100 MHz [4]. To approach this, we applied a balanced detector with changeable gain and bandwidth settings (PDB450C, Thorlabs) set to 150 MHz with 10^3 V/A transimpedance gain. A balanced detector also has an advantage over the single detectors in that the quantization error applies to the difference signal. A schematic of the improved setup (system 2) along with the one (system 1) investigated in [3] is shown in Fig. 1. All optical paths were fiber coupled with multi mode (MM) fibers (FG105UCA, Thorlabs) and a fused fiber optic coupler (TM105R5F1B, Thorlabs) to split the original pulse into sample and reference paths. For transmission, the fibers were cleaved and glued in a specialized holder based on v-grooves, where the sample drop could be sucked away from below with fitted tubing.

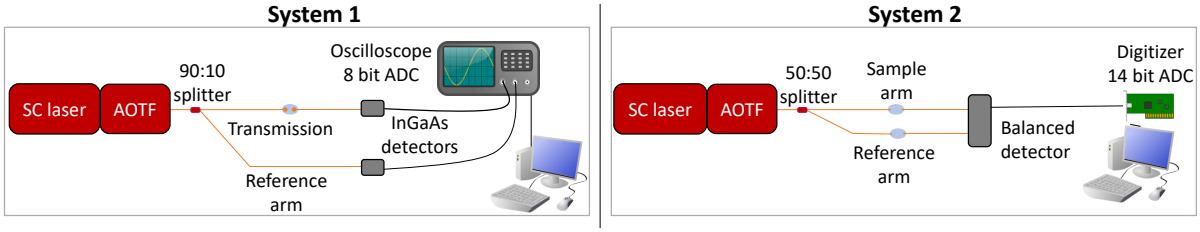

Fig. 1. Schematic of the system setups investigated.

The common mode rejection ratio (CMRR) for a balanced detector is defined as

$$\mathrm{CMRR} = 20\log_{10}\frac{V_{\mathrm{unbal}}}{V_{\mathrm{bal}}}, \tag{1}$$

where V_{unbal} is the unbalanced output without signal in one of the arms, and V_{bal} is the balanced output. The CMRR of the PDB450C was found experimentally to be between 17 dB and 23 dB when directly fiber-coupled (tabulated to 25–30 dB by the Thorlabs). The relatively poor balance is due to the fused coupler (45–55 % split).

In initial measurements of the balanced setup with transmission through water in both arms, an average $V_{\mathrm{bal}} = 54.1\,\mathrm{mV}$ and $V_{\mathrm{unbal}} = 394.8\,\mathrm{mV}$ integrated over the pulse were found for 1410–1660 nm. The measurements acquired in the balanced mode had an average variance of 4.8 %, corresponding to an average of 2.6 mV. The average CV from the full input was 0.8 % and the average CMRR was 16 dB. If the CMRR is improved to 30 dB, the average CV can be estimated to 0.15 % across the wavelength range. This is a slight improvement compared to system 1, which measured single-wavelength CV down to 0.56 % after the RIN was accounted for [3].

Table 1. Estimated noise limitation contributions from system components. The RIN suppression was measured (1410–1660 nm). The detector noise is referenced to 80 % of the saturation power.

Limitation	Component	CV
Quantization noise	ADC 8 bit	0.39 %
	ADC 14 bit	0.006 %
RIN	Directly from SuperK	3.2 %
	Reference arm, directly from laser, two DET01	1.2 %
	Reference arm, balanced through water, PDB450C	0.8 %
Detector noise	DET01	1×10^{-10} %
	PDB450C	2×10^{-6} %

The noise contribution from the components are shown in Table 1. Using a 14 bit ADC, the limiting factor is how well the RIN can be canceled. The value for the balanced detector has improvement potential by better balancing. With the high-speed digitizer, it is unproblematic to average across several pulses to decrease the variance by an additional $\sqrt{N}$ and therefore obtain a required accuracy of less than 0.03 % variation across the laser intensity.

In initial measurements, the variance between water spectra (re-applied between measurements) was 1.25 %, indicating that there are environmental factors that must be improved upon to reach the desired accuracy. These limitations may lie in the fixation of the fiber for transmission, or effects of temperature variations within the room on the dispersion and power distribution from the fiber optic coupler to the signal and reference arm. We conclude that system 2 has the potential to achieve the required SNR for accurate acqueous glucose detection.

References

1. M. Ren, M. A. Arnold, "Comparison of multivariate calibration models for glucose, urea, and lactate from near-infrared and Raman spectra," Anal. Bioanal. Chem. (2007); 387(3): 879–888. DOI: 10.1007/s00216-006-1047-4.
2. R. R. Alfano, "The Supercontinuum Laser Source: The Ultimate White Light; 3rd ed.; Preface", Springer (2016), ISBN 978-1-4939-3326-6.
3. S. S. Fuglerud, K. Milenko, R. Ellingsen, A. Aksnes, D R. Hjelme, "Feasibility of supercontinuum sources for use in glucose sensing by absorption spectroscopy," Proc. SPIE 11073, (19 July 2019); doi: 10.1117/12.2524005.
4. R. M. Kurtz, Thomas C. Forrester, "Optimizing reception bandwidth of a pulsed signal," Proc. SPIE 11410, Laser Radar Technology and Applications XXV, 114100B (23 April 2020); doi: 10.1117/12.2558339