Non-invasive blood glucose monitoring using an optical bridge: correction for mechanical error

HANNU HARJUNMAA* AND SINIKKA HARJUNMAA

Valoa Technologies, Inc., 14 Damon Road, Holden, MA 01520, USA

**president@valoatechnologies.com*

Abstract: The near-infrared optical bridge non-invasive blood glucose monitor has been long in development. It is a doubly differential photometer that makes use of dynamic blood content modulation effects. During a 2014 clinical trial, a mechanical irregularity was uncovered that affected the entire series of eight prototypes. Although it was not known at the time, it turned out that it was possible to correct the data to substantially remove the effects of the irregularity. A significant improvement in blood glucose measurement accuracy ensued.

OCIS codes: (170.0170) Medical optics and biotechnology; (170.3890) Medical optics instrumentation; (230.0230) Optical devices.

1. Introduction

Non-invasive blood glucose monitoring can be done within many modalities [1, 2]. In the near-infrared realm, the Optical Bridge doubly differential photometer may be used in transmission mode or in back-scattering mode to measure blood glucose in the bloodstream [3]. Usually, in the transmission mode the monitored part is the earlobe; in the back-scattering mode, it is the fingertip. This analysis uses earlobe measurements.

The Optical Bridge uses the near-infrared wavelength range that includes the glucose absorption band at about 1620 nm (there are no sharp spectral features in this wavelength range; all in vivo absorption spectra are dominated by the absorption of water, which has a broad peak at about 1460 nm).

The data used in this analysis was obtained in a clinical study by Grove Instruments, Inc., of Worcester, MA. 13 adult test subjects of both sexes were involved, both T1D and T2D.

2. Method

2.1 Detailed description

The Optical Bridge uses laser diodes as light sources and an InGaAs photodiode as the detector. The laser diodes are adjusted to send two different wavelengths into the sample, alternating in time, having the same extinction in the tissue background (in the transmission mode, two different thicknesses are required to establish equal extinction). One of the wavelengths is absorbed by glucose; the other is not. The reference wavelength is actually composed of two

different wavelengths that are mixed in order to produce the desired intensity-weighted balanced reference wavelength [4].

In order to separate the glucose signal from the background, the blood content of the sample volume is modulated by squeezing the sample. Without modulation, the glucose signal would be indistinguishable from the background.

Signals are recorded during the change in blood content in the sample volume, during the in-squeeze, and during the "decay" after unsqueeze, as blood fills the sample volume with a time constant of the order of one second, at constant thickness. Each record consist of 2760 data points at the two bridge wavelengths, plus at a green (525 nm) wavelength set up to measure the actual blood content independently.

The features used to derive the glucose concentration are slopes of the IR difference signal vs. green signal, with added information from other signals available in the system. The glucose information within the slopes is protected three-fold: 1) even if the Optical Bridge is not perfectly balanced, it is only the magnitude of the bridge signal, not its slope, that is affected, 2) the speed of blood entry does not affect the slope (changing speeds in IR and green cancel), and 3) the depth of blood modulation, although it does have an effect on the accuracy through base length, does not affect the slope in the first approximation.

A 16-bit A/D converter is used to digitize the signals. In a DC measurement, a 16-bit resolution would not be adequate to measure blood glucose (the extinction by the background is about 1500 times the absorption of 100 mg/dl of glucose), but using slope features increases the actual resolution by more than three orders of magnitude, sufficient to quantify blood glucose with a resolution of the order of 10 mg/dl.

The Optical Bridge method uses interval quantities, not absolute quantities. The method does not rely on sample or device properties to remain constant from one measurement to the next; however, it does require those properties to remain reasonably constant during the 10 seconds that it takes to collect the data.

Because the measurement is done only on the change of the differential bridge signal, any residual glucose in the background does not matter; it becomes part of the background. In other words, the method measures glucose in the bloodstream, which is of capital importance and which many other methods cannot do, as they are affected by the glucose in the interstitial fluid.

The Optical Bridge is balanced for each measurement, so changes in the background, to be expected even on the same subject and same earlobe, are largely accommodated by the balancing process.

Two kinds of prototypes have been built: hand-held battery-operated, and Development Platform, where IR, power and communication are routed in a fiber/cable bundle from a central unit to a handset similar to the battery-operated unit.

2.2 Mechanical irregularity

The Development Platform prototype incorporates a mechanical encoder that registers the actual position of the measurement head. An inspection of the encoder data revealed that the measurement head did not move as intended: when opening, it almost always got stuck before reaching its intended position, thereby causing the IR and green signals to be higher than they should have been and causing a disruption in the signals dependent on blood refilling.

The recording of the actual position of the measurement head makes it possible to correct the IR and green signals by extrapolation to values they would have had if the movement of the measurement head was correct. Obviously, the corrected data is not quite as good as the data would have been if the movement were correct in the first place, but it is much better than the corrupted data. In the corrected data, the data windows that delimit where the features are calculated, were readjusted to cover the corrected regions. Some other related parameters were re-optimized.

3. Results

Measurement protocol Atlas was used in 48 5-hour sessions of 31 measurements each, yielding a 1488-measurement data set. Both ears of each subject were measured, producing two sessions per subject-day. The reference blood glucose value was obtained by fingerprick using a HemoCue blood glucose analyzer.

The Atlas measurement protocol consists of a series of light squeezes and unsqueezes on the earlobe, with the optical signals being recorded during the movements and during the stationary intervals between the movements.

The effect of the correction was tested using Leave-One-Out Cross-validation (LOOCV) on the 48 sessions separately. The comparison of the original and the corrected results is shown in Table 1. No data was rejected, and all 1488 data pairs are included in the analysis. MARD = Mean Absolute Relative Deviation.

Table 1. LOOCV results before and after correction

	Original	Corrected
median Pearson's r	0.416	0.709
median p-value	0.02	$8.3 \cdot 10^{-6}$
median MARD %	17.9	14.5
number of statistically significant ($p<0.05$) session correlations out of 48	31	48

Of the 48 sessions, all but one of the session glucose correlations improved and only one deteriorated. If we consider an improvement in correlation a success, the p-value for 47 successes in 48 trials is $1.7 \cdot 10^{-13}$. After the correction, all 48 sessions have a p-value of <0.05. The smallest p-value is $8.7 \cdot 10^{-13}$, corresponding to the highest corrected r of 0.913. The effect of the correction is shown in Fig. 1.

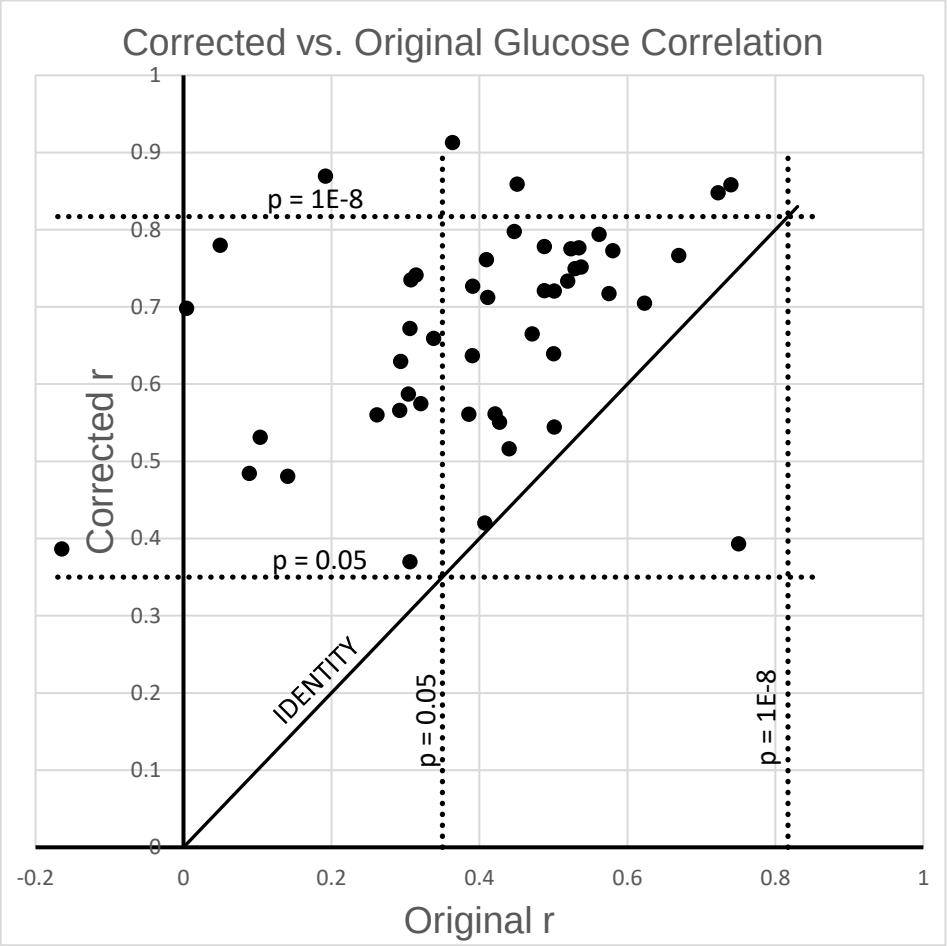

Fig. 1. The 48 sessions showing their original and corrected glucose correlations. If a session marker has moved up from the identity line, the correlation has improved; if it has moved down, it has deteriorated.

4. Discussion

It would be tempting to compare these results with those of Ref. 3, where the correction was not used. However, there are practical difficulties. The LOOCV method was chosen here, because the main issue is comparison, and LOOCV makes for more reliable comparisons, as it uses the entire data set. Also,

- The Ref. 3 dataset is a much smaller subset of this dataset (620 data pairs; our dataset is larger because the study continued after submission of [3])
- Ref. 3 had 63 measurements rejected for laser instability.

We can try to make projections. The Ref. 3 MARD in day-to-day prediction is 19.7 % for the 10 test subjects and 13.4 % for a select subset of 6 test subjects with better perfusion. According to our results, the improvement resulting from the correction is 17.9 % to 14.5%, or a reduction factor of 0.81. Therefore, if the performance changes in proportion in the two methods, Ref. 3 could have reported an MARD of 16.0 % and 10.9 %.

We are ignoring the fact that our data set contains measurements that were rejected in [3]; we are including all of our measurements in order to make our estimate very conservative. It is also hard to identify the previously rejected measurements with certainty. If we had rejected those measurements, the reduction factor would be even smaller and the true prediction performance even better.

5. Conclusion

These results prove that Optical Bridge technology remains a viable option for non-invasive blood glucose monitoring. The next clinical study will use a revised squeeze mechanism that does not suffer from irregularities.

Funding

Funding for this work was provided internally by Valoa Technologies, Inc.

Disclosures

In January 2016, Valoa Technologies, Inc. acquired the IP of the defunct Grove Instruments, Inc., related to the non-invasive measurement of blood glucose using the Optical Bridge. The lead author of this paper was Co-Founder and Chief Scientist of Grove Instruments, Inc., and is the originator of Optical Bridge technology.

References

1. A. Navaz, P. Øhlckers, S. Sælid, M. Jacobsen, M. Nadeem Akram, “Review: Non-invasive Continuous Blood Glucose Measurement Techniques”, in Journal of Bioinformatics and Diabetes, Vol. 1(3), 1-27 (2016)

2. H. Harjunmaa, S. Kun, R.A. Peura, J. Rolls, Non-invasive substance concentration measurement using an optical bridge, US Patent 7,003,337

3. Combs A., Rawson B., Keating J., Burrell R.A., Schurman M., Lock J.P., “Optically Based Noninvasive Glucometer Demonstrates Clinical Trend Accuracy Durability 24 Hours After Calibration”, in Abstracts from ATTD 2015 8th International Conference on Advanced Technologies & Treatments for Diabetes, (Mary Ann Liebert, 2015), abstract 88.

4. H. Harjunmaa, S. Kun, R. Burrell, G. Leuenberger, US Patent 8,175,666