



---

The Space Congress® Proceedings

1995 (32nd) People and Technology - The Case  
For Space

---

Apr 26th, 2:00 PM - 5:00 PM

## Paper Session II-B - Optical Diagnostics: Reagentless Chemistry for Extended Space Flights

Glenn M. Cohen  
*Department of Biological Sciences*

Fredric M. Ham  
*Division of Electrical and Computer Engineering*

Brent R. Gooch  
*Holmes Regional Medical Center*

Follow this and additional works at: <https://commons.erau.edu/space-congress-proceedings>

---

### Scholarly Commons Citation

Cohen, Glenn M.; Ham, Fredric M.; and Gooch, Brent R., "Paper Session II-B - Optical Diagnostics: Reagentless Chemistry for Extended Space Flights" (1995). *The Space Congress® Proceedings*. 22. <https://commons.erau.edu/space-congress-proceedings/proceedings-1995-32nd/april-26-1995/22>

This Event is brought to you for free and open access by the Conferences at Scholarly Commons. It has been accepted for inclusion in The Space Congress® Proceedings by an authorized administrator of Scholarly Commons. For more information, please contact [commons@erau.edu](mailto:commons@erau.edu).

**EMBRY-RIDDLE**  
Aeronautical University™  
SCHOLARLY COMMONS

## Optical Diagnostics: Reagentless Chemistry for Extended Space Flights

<sup>1</sup>Glenn M. Cohen, <sup>2</sup>Fredric M. Ham, and <sup>3</sup>Brent R. Gooch

<sup>1,2</sup>Florida Institute of Technology, <sup>1</sup>Department of Biological Sciences <sup>2</sup>Division of Electrical and Computer Engineering, Melbourne, FL, <sup>3</sup>Holmes Regional Medical Center, Melbourne, FL

### ABSTRACT

Maintaining the health and safety of the crews of spacecraft remain the highest priorities. Health monitoring requires at least two overlapping activities: (1) frequent or continuous monitoring of bodily functions to determine normalcy or deviation from normalcy, and (2) specific diagnosis and treatment of diseases. Thus, with a broad mandate and limited resources, the spacecraft must provide the diagnostic capabilities for quickly and accurately diagnosing a wide range of diseases. Optical devices, though still in the early developmental stages, diagnose diseases by analyzing and quantitating the spectra of metabolites and other substances non-invasively and without using chemical reagents. Once commercially available, optical devices will replace many clinical tests that use chemical reagents for diagnostics.

### INTRODUCTION

Ensuring the health of crews is essential for the successful completion of the various tasks of missions. Although crews are thoroughly examined and treated for their diseases prior to missions, they are subjected to various stresses during flights that can increase their susceptibilities to diseases. For extended missions, the spacecraft must stock an inventory of different diagnostic kits (each containing its own specific reagents) and medications in order to test for and treat a broad range of diseases accurately and quickly. The diagnostic kits and devices must conform to the constraints imposed by size, weight, and power consumption. After their use, the spacecraft must safely store or degrade the chemical reagents, blood and other body fluids, and non-reusable devices. In contrast, optical devices perform diagnoses non-invasively, do not require samples of blood or body fluids, can operate almost continuously, and use no reagents or supplies. Optical devices offer advantages for extended missions not provided by test kits that use chemical reagents.

We are developing an optical device using near-infrared spectroscopy for monitoring blood chemistry (glucose) non-invasively (without drawing blood). This technique, sometimes called "reagentless chemistry" involves identification and quantitation of the spectra of different chemicals in the blood. When fully developed, the patient will illuminate a finger (Fig. 8), ear lobe or other optically translucent area and sensor detects the spectral signals on the other side. Using signal processing techniques, background noise is removed and spectral signal are quantitated (Ham, 1994; Ham et al., 1994).

For our research on blood glucose, we felt that the non-invasive device had to meet at a minimum of three requirements: (1) measures the substance in the blood directly using a safe, low-intensity, near infrared source; (2) determines concentrations of blood substances using an artificial neural network and signal processing techniques, and (3) measures the substance in the blood independently of both skin pigmentation and the finger site where the light impinges.

### METHODOLOGY AND PRELIMINARY RESULTS

#### The Data Sets and the Baseline Corrections

A very comprehensive data set, consisting of 1251 near infrared (NIR) spectra of human blood serum, has been generated by Miles, Inc. (Non-Invasive and In-Licensing Diabetes Business Unit).

This data has been acquired by our research team, and has been the basis for our research during the past year. The NIR data set of human blood serum gathered from hospitalized patients consists of 834 spectra for which reference glucose data was determined for each sample using a YSI (Yellow Springs Instruments) laboratory glucose analyzer (instrument error  $\leq 2\%$ ). The remaining 417 spectra for prediction do not have any reference glucose data. The data were gathered with a modified NIRsystems 6500 model spectrophotometer over the wavelength region from 1100 nm to 2498 nm ( $9091\text{ cm}^{-1}$  to  $4003\text{ cm}^{-1}$ ) with a spectral resolution of 2 nm. The region from 1888 nm to 2428 nm ( $5297\text{ cm}^{-1}$  to  $4119\text{ cm}^{-1}$ ) is the most significant for determining glucose concentrations. There are 3 significant glucose absorption bands in this region which are combination bands associated with C-H stretching vibration transitions. This can be seen by observing Fig. 1 which shows the NIR absorption spectrum of anhydrous glucose in this spectral region. Miles, Inc. also supplied us with a data set consisting of 99 spectra of glucose in a simple aqueous matrix (water). The first 9 spectra were for water alone, and these were averaged and used to remove the intrinsic high background absorption due to the water. This was performed by logarithmically (according to the Lambert-Beer law) subtracting the averaged water spectrum from the remaining spectra. Figure 2 shows the NIR spectra of water. Note the large absorption band centered around  $5200\text{ cm}^{-1}$ . However, the water does not absorb much energy in the region where glucose has predominate absorption bands (see Fig. 1).

The same process was carried out for the blood serum data. This is also necessary in the case of the blood serum data because there doesn't exist a *matrix-matched* background spectrum available to use in processing the data (Ham et al., 1994a). This is precisely our systematic incremental complexity testing strategy, to develop *one-step-at-a-time* the matrix-matched background spectrum that will eventually yield, upon removal from the raw spectrophotometric data, that information which is associated with only glucose. This will involve obtaining NIR spectra for other blood constituents that have absorption characteristics in the same spectra region of glucose.

#### Preprocessing and the Statistical Approach

Therefore, the first step in this process is to use the aqueous water matrix as the artificial background spectrum for the blood serum NIR spectroscopic data. As a basis of comparison, the water NIR spectrum was first removed from the glucose in water NIR spectra. A very powerful statistical modeling method, known as partial least squares (PLS) regression, was used to predict the glucose concentrations from NIR spectra used as monitoring (or test) data. The model is first developed (or trained) using a subset of the data (NIR spectral samples along with the associated reference glucose concentrations) and then tested on the remaining subset of NIR spectra. Therefore, 48 of the samples were used for training and 41 were used for testing (monitoring). One of the samples was removed from the global data set because it was determined to be an outlier. The predicted glucose concentration values are then compared to the actual reference values to establish the accuracy of the developed model. Figure 3 shows the prediction results using the trained PLS model for the *raw* data (essentially the same spectral region was used for the blood serum data). The PLS model required 5 factors and the mean percent training error (MPTE), where  $MPTE = 5.13\%$  (11.18 mg/dl) and the mean percent monitoring error (MPME),  $MPME = 12.71\%$  (21.78 mg/dl), respectively. It is obvious from these results (and observing Fig. 3), that there is a considerable amount of error associated with the predictions made by the PLS model. However, the PLS model can only be as good as the data that is given for training. Therefore, if the data are pre-processed (digitally filtered) to remove the baseline variations and the high frequency noise then the PLS model will be more accurate when trained by the less noisy data (Arnold and Small, 1990). The filtering process involves coupling a digital 3rd-order Butterworth

filter with the PLS regression method in an optimization process to simultaneously minimize the MPTE and MPME (Ham et al., 1994b). The procedure searches over defined ranges of the digital filter parameters and the number of PLS factors, to yield the best combination of filter parameters and PLS factors such that the MPTE and MPME are minimized. Figure 4 shows the results after the optimal filtering process for 7 PLS factors and the digital filter parameters: center frequency = 0.2158f and bandwidth = 0.1992f. For the filtered data results, the MPTE = 3.13% (7.02 mg/dl) and the MPME = 4.43% (11.52 mg/dl). Therefore, the filtered data results in much better results than the raw data. This is a result of removing the baseline variations and the high frequency noise in the data with the optimal digital filter (and also the selection of the optimal number of PLS factors).

#### Determination of Glucose Concentrations

Figure 5 shows the NIR spectrum of a one sample from the blood serum data set (for 605 mg/dl reference glucose). Note that the absorption peaks that were prominent for the anhydrous glucose in Fig. 1 are now somewhat *smear*ed. This is due to hydrogen bonding and interference from other molecules in the serum. However, the glucose bands are still recognizable. A PLS model was developed on 509 NIR spectra, and tested on 301 (the results are shown in Fig. 6). There were 24 outliers removed from the data set of 834 NIR spectra. Using the artificial background spectrum consisting of only water, the PLS prediction results are reasonable, but not acceptable for reliable glucose concentration predictions in a non-invasive monitoring system, especially for the hypoglycemic diabetic condition. A standard performance level for predicting glucose concentrations has not been established as yet. However, we feel that the diabetic hypoglycemic condition should dictate this standard performance level, and a mean percent error  $\leq 5\%$  is a reasonable value. Therefore, the MPME = 11.01%, or 20.8 mg/dl as shown for the prediction results in Fig. 6 would not be acceptable based on the above suggested standard. This further reinforces the need for an increasing complexity testing scenario which will incrementally *build* the matrix-matched background spectrum for blood serum data, and ultimately for whole human blood. An integral part of this process is a technique that we have developed using the PLS regression calibration model building method. The PLS regression method involves a series vector projections of reference concentration information on *principle* PLS vectors in an abstract vector space. We have exploited these interrelationships that are utilized in the model building process for the PLS regression method and used them to extract very fine features of the spectroscopic data which are subtly related to the information that is sought, namely, glucose, and specifically the amount of the substance in a sample, i.e., the actual concentration. Figure 7 shows a 3-dimensional depiction of the use of 3 PLS *principle* vectors. The entire data set samples were averaged over each glucose concentration group (this subgroup consisted of 287 averaged samples), and the 3 PLS *principle* vectors were used to extract the salient glucose features from the data. The same process was carried out on the entire group of samples. Figure 7 shows how this extracted spectral information is basically related to the glucose reference concentration information by plotting the samples in 3-dimensional space. The *sample trend* corresponds directly to the regression results in Fig. 6. This is a very powerful method of extracting as much information from the spectroscopic data with a limited matrix-matched background spectrum. Therefore, as the matrix-matched background spectrum is enhanced through the incremental complexity testing process, the PLS regression prediction results will continuously improve to the point that the  $\leq 5\%$  error figure can be met.

#### DISCUSSION

Buerk (1993) listed the behaviors of an ideal biosensor as follows: (1) high effective sensitivity, (2) ease of calibration, (3) linearity of sensitivity, (4) high limit of detection, (5) quantifiable background signal, (6) negligible hysteresis, (7) low drift and high long-term stability, (8) high

selectivity [low interference], (9) fast dynamic response, (10) temperature compensation, (11) high-signal-to-noise ratio, (12) long and predictable lifetimes, (13) safety and biocompatibility. Although these generic behaviors are shared among biosensor types, such as electrochemical, enzyme-based, and optical, only optical sensors can monitor blood chemistry non-invasively (Fig. 8) and without using chemical reagents. In short, optical sensors offer an advantage for routine tests that are frequently performed, such as glucose monitoring, and for extended space missions.

Oximetry, a non-invasive technique, is widely used for monitoring oxygen levels in blood. Optical sensors detect the spectral properties of oxygenated and deoxygenated hemoglobin and quantitate the spectra (Buerk, 1993; pgs. 137-139). The oxygen signal is strong because of the high concentration of hemoglobin in the blood. By comparison, most other chemicals in the blood are difficult to monitor because of their extremely low concentrations and overlapping spectra with other chemicals. Thus, the detection and prediction of the spectral signals of most blood chemicals requires far more elaborate signal processing than for monitoring oxygen levels.

A robust discrimination strategy which can detect and predict glucose concentrations with an acceptable level of accuracy using spectrophotometric methods serves as a pivotal element in a highly reliable non-invasive monitoring system for measuring blood glucose (and other substances). Many technical obstacles must be overcome in developing an optical system, such as: (1) removal of baseline variations that instrumentation drift and ambient conditions introduce into the spectroscopic data (Hazen et al., 1994; Small et al., 1993), (2) intrinsic high background absorption due to water, (3) high frequency noise due to the detector and removing the background absorption due to water, (4) optical properties of skin (scattering of light), which is an anisotropic and inhomogeneous medium (Anderson and Parrish, 1982), (5) large numbers of overlapping absorption spectra and molecular interactions of other blood constituents with glucose, and (6) degradation of signal of interest due to interference of other blood substances, i.e., red blood cells (45% of blood volume).

To date, we have overcome many of the technical obstacles described above and quantitated levels of blood glucose ranging in concentration from 0 to 600 mg/dl (100 mg/dl is the normal value) (see Figs. 1-7). The development of the technique of optical monitoring of blood chemistry represents a high priority for people with diabetes who presently must prick their fingers several times each day to monitor blood glucose using chemical reagents (Robinson et al., 1992). Optical technologies are transferable to many other diagnostic applications, particularly for extended space missions. An optical device, which can function over wide spectral ranges, can replace a single diagnostic test kit that is frequently used or replace many different types of test kits.

#### ACKNOWLEDGMENTS

The research was supported by a research grant from Holmes Regional Medical Center, Melbourne, FL.

#### REFERENCES

- Anderson, R.R. and J.A. Parrish. 1982. Optical properties of human skin. In: *The Science of Photomedicine*. (J.D. Regan and J.A. Parrish, eds.). Plenum Press, New York. Pgs. 147-194.
- Buerk, D.G. 1993. *Biosensors: Theory and Applications*. Technomic Publ. Co., Lancaster, PA.
- Hann, F.M. 1994. Detection and classification of biological substances using infrared absorption spectroscopy and a hybrid artificial neural network. *J. Artif. Neural Networks* 1, 101-114.
- Hann, F.M., G.M. Cohen, K. Patel, and B.R. Gooch. 1994. Multivariate determination of glucose using NIR spectra of human blood serum. In: *Proc. 16th Ann. IEEE Engineer. Biomed. Conf. (J.H. Nagel and W.M. Smith, eds.)*.

LRW Publ., Laurel, MD. Vol. 16, Part 2, Pgs. 8118-819.

Hazen, K.H., M.A. Arnold, G.W. Small. 1994. Temperature-insensitive near-infrared spectroscopic measurement of glucose in aqueous solutions. *Appl. Spectrosc.* 48, 477-483.

Robinson, M.R., R.P. Eaton, D.M. Hasland, G.W. Koepf, E.V. Edward, B.R. Stallard, and P.L. Robinson. 1992. Noninvasive glucose monitoring in diabetic patients: preliminary evaluation. *Clin. Chem.* 38, 1618-1622.

Small, G.W., M.A. Arnold, and L.A. Marquardt. 1993. Strategies for coupling digital filtering with partial least-squares regression: Application to the determination of glucose in plasma by Fourier transform near-infrared spectroscopy. *Anal. Chem.* 65, 3279-3289.

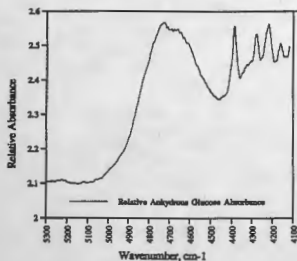


Figure 1. NIR spectrum of anhydrous glucose.

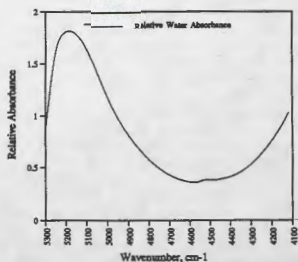


Figure 2. NIR spectrum of water.

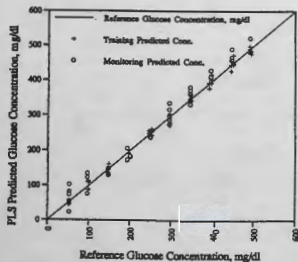


Figure 3. PLS prediction performance results for the raw glucose in water data.

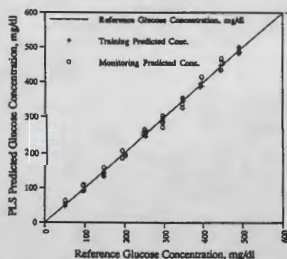


Figure 4. PLS prediction performance results for the optimally filtered glucose in water data.

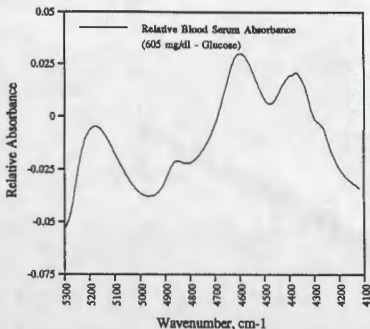


Figure 5. NIR spectrum of blood serum (605 mg/dl - Glucose) with water spectrum logarithmically subtracted.

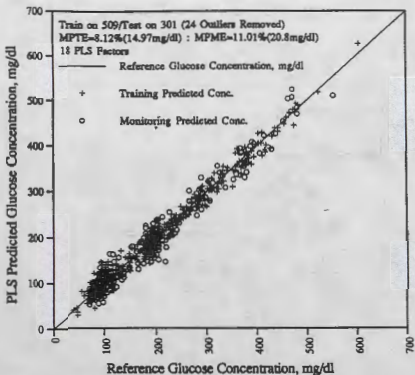


Figure 6. Partial least-squares prediction of blood serum glucose using 18 PLS factors. Training was performed on 509 samples and monitoring (testing) on 301 samples.

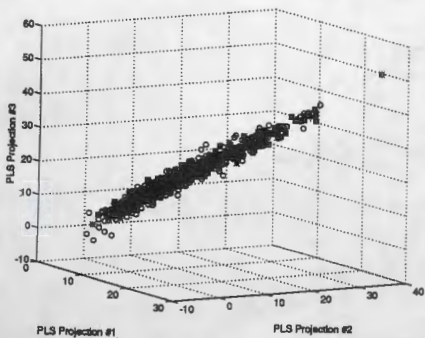


Figure 7. Three PLS projections on the training and monitoring data.

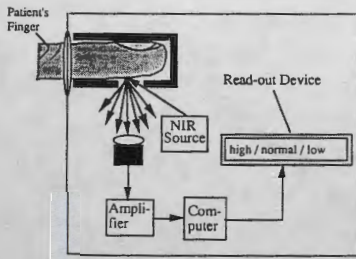


Figure 8. Monitoring box (the read out device will display a quantitative measure of the actual glucose levels in mg/dl).