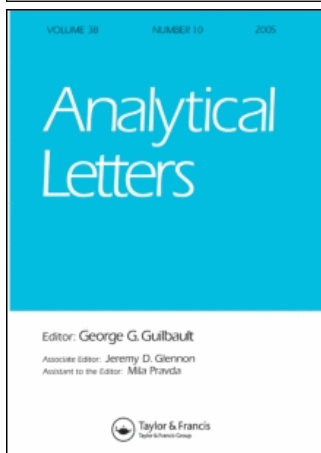


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ACCURACY OF THE YSI STAT PLUS ANALYZER FOR GLUCOSE AND LACTATE

Key Words: Glucose, Lactate, Biosensors, Calibration, Accuracy

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ABSTRACT

The YSI model 2300 Stat Plus analyzer accurately measures glucose in aqueous solutions with an overall standard error of prediction (SEP) of 0.28 mM and a mean percent error (MPE) of 1.79 %. The absolute and relative errors for glucose measurements are concentration dependent. Initial measurements demonstrate the need to periodically monitor the accuracy of this analyzer to avoid systematic errors. Lactate is measured with an overall SEP of 0.18 mM and MPE of 5.10 %. Analysis of the residuals indicates a slight negative bias of -0.07 mM for lactate.

INTRODUCTION

The analytical utility of using near infrared (NIR) spectroscopy for clinical chemistry is being evaluated by many research groups.¹⁻⁴

The concept is to obtain the concentration of specific analytes in clinical samples, mainly blood and serum, by analyzing the NIR spectrum of the sample. Because of the complexity of the sample matrix and the overlapping nature of NIR spectra, multivariate calibration methods, such as partial least squares (PLS) regression, principal components regression (PCR), and artificial neural networks (ANN) are needed to effectively extract the analytical information from the spectral information. Each of these algorithms requires a set of calibration, or training, spectra which consists of a series of NIR spectra with known analyte concentrations. Ultimately, the accuracy of the NIR spectroscopic method will be limited by that of the reference method used to establish analyte concentrations in samples used to build the calibration model.

Particular attention has been given to the NIR spectroscopic measurement of glucose. This effort has been fueled by the possibility of measuring blood glucose in a noninvasive manner by analyzing NIR spectra taken through a vascular region of the body. Progress in developing a noninvasive blood glucose analyzer depends on availability of a convenient and reliable reference method for blood glucose measurements.

The Yellow Springs Instrument (YSI) model 2300 Stat Plus Glucose and Lactate Analyzer is an FDA approved instrument for measuring glucose and lactate in human blood samples. Biosensors are used to measure these analytes after the sample is diluted. The ease of operation, low cost, and rapid throughput of this analyzer

makes it ideally suited as a reference method for NIR spectroscopy methodology development. Accuracy of this analyzer must be firmly established, however, before it can be used extensively for building complex multivariate calibration models. Accuracy of the original YSI model 23A glucose analyzer was established by comparing results to those obtained by the hexokinase method for glucose.⁵ Subsequent instruments have been compared to earlier instrument models.

Accuracy of the model 2300 YSI analyzer for both glucose and lactate has been established and is reported in this paper. The resulting standard errors of prediction (SEPs) represent minimum values possible for any NIR spectroscopic method that relies on this instrument for reference values.

EXPERIMENTAL

Apparatus and Reagents

Measurements were made with a YSI model 2300 Stat Plus Glucose and Lactate Analyzer in conjunction with a YSI model 2710 turntable. A Perkin-Elmer 141 polarimeter was used to establish the enantiomeric distribution of L and D lactate. A Mettler AE-163 analytical balance was used to prepare all standard solutions.

Standard solutions were prepared by using reagent grade preparations of D-glucose (99.9% purity) and either lithium lactate (99.67% purity) or sodium L-lactate (99.6% purity). The lithium lactate was a mixture of both D and L isomers, whereas, the sodium lactate was essentially pure L-lactate. All reagents were purchased

from common suppliers. Glucose and lactate preparations were dried to a constant mass at 85 °C before use. All solutions were prepared with distilled-dionized water obtained by passing the house distilled water through a Milli-Q three house purification unit.

Procedures

All solutions were prepared with a working buffer composed of 0.1 M monosodium phosphate and 0.044% 5-fluorouracil maintained at pH 7.4. Stock solutions of glucose and lactate were prepared. The lithium lactate was determined to be a racemic mixture ($49.5 \pm 0.5\%$). Fifty-six solutions were prepared by diluting different volume combinations of the glucose and lactate stock solutions with working buffer. Nineteen other solutions were prepared with lactate and no glucose. All solutions were permitted to equilibrate overnight before use.

All samples were analyzed in triplicate except one where an additional measurement was needed to clarify an inconsistent result. The YSI analyzer was operated in the standard 5/15 calibration mode with the 2710 turntable. In this mode, the instrument is automatically calibrated every 15 minutes or after every 5 samples. A one-point calibration is used for each analyte and the concentrations are 10.0 mM glucose and 5.00 mM lactate. During operation, the sample is aspirated through the sipper arm and directed into the measurement chamber where it is diluted with buffer and the measurement is made. The buffer used with the YSI analyzer was composed of 0.01227 M

monosodium phosphate, 0.05427 M disodium phosphate, 0.001668 M EDTA (disodium salt), 0.007149 M sodium benzoate, and 0.05214 M sodium chloride. A strip chart recorder was connected to the analyzer and, in some cases, the electrode outputs were recorded as a function of time.

RESULTS AND DISCUSSION

During the routine operation of our YSI analyzer, we noted that values from the analyzer were consistently low when standard glucose solutions were analyzed. Upon further investigation, we uncovered a systematic negative bias for glucose values over a concentration range from 1 to 43 mM. The data presented in Figure 1 show the extent of this bias. Regression analysis of the correlation plot in Figure 1 reveals a slope of 0.958 ± 0.002 , a y-intercept of 0.1 ± 0.5 mM and an R-square value of 0.9972. A systematic error is indicated by this sub-unity slope. The extent of the error is better illustrated by the residual plot presented as the Figure 1 inset. This plot reveals a strong negative bias over the entire concentration range. For the 398 total measurements completed, 373 (94%) had negative errors. Across the entire data set, the standard error of prediction (SEP) is 0.83 mM and the mean percent error (MPE) is 3.64%.

The unacceptable systematic error illustrated above was eliminated by replacing all components of the sampling mechanism (tubing, sipper arm, and gaskets). This analyzer is designed with

Glucose Correlation Plot

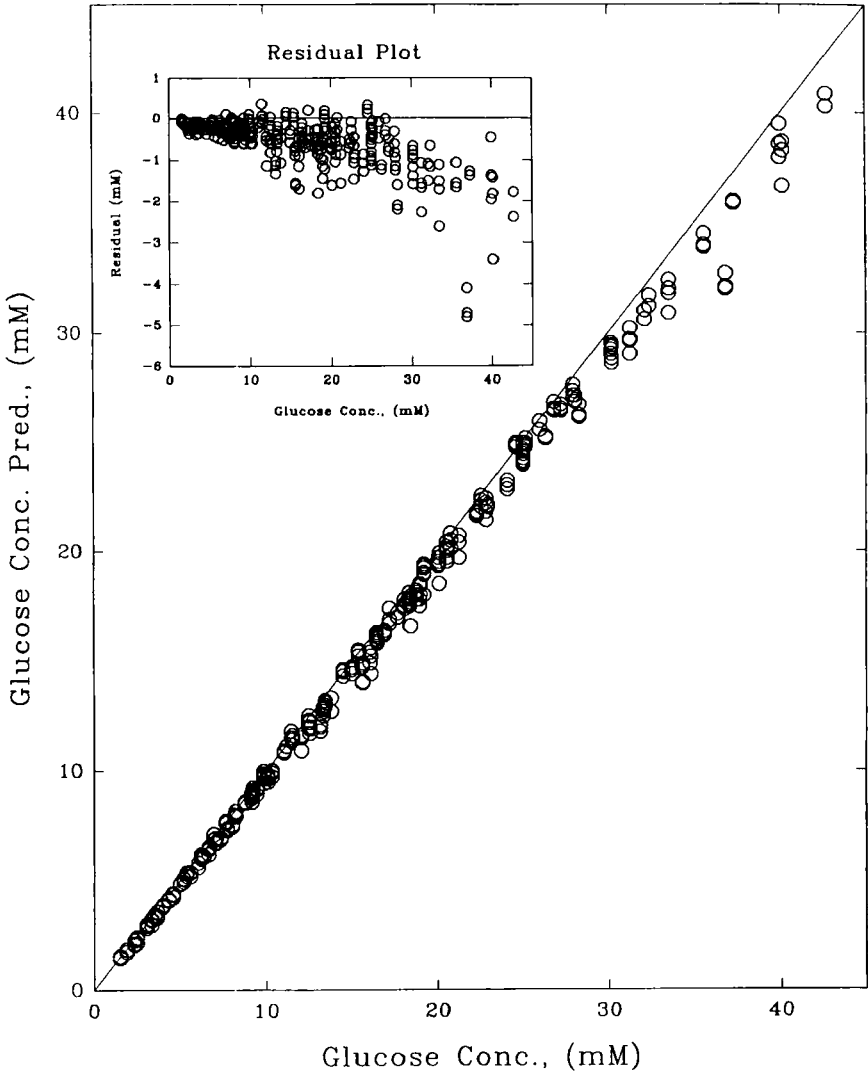


Figure 1. Correlation plot for glucose before instrument modifications. Solid line shows the ideal unity line. Inset shows the corresponding residual plot.

different paths for the calibration solution and the sample solutions. Apparently, the plumbing associated with drawing either the sample or calibrant was fouled, thereby creating a negative bias by failing to aspirate the correct volume of solution.

No systematic errors could be identified for glucose once the sampling components were replaced. The correlation and residual plots shown in Figure 2 illustrate this point. Regression analysis of the correlation plots indicates a slope of 1.007 ± 0.003 , y-intercept of -0.1 ± 0.3 mM, and R-square value of 0.9986. Of the 168 samples tested, 82 (49%) give positive residuals and 86 (51%) give negative residuals. Further inspection of the residual plot reveals larger absolute errors at higher concentrations. This trend is also indicated by higher SEP values when computed with only high glucose concentrations. Table 1 summarizes values of SEP and MPE for different glucose concentration ranges. Although the SEP is larger at the higher concentrations, the relative error, as measured as the MPE, decreases at higher concentrations. Over the entire concentration range, for all 56 samples and 168 measurements, the SEP is 0.28 mM and the MPE is 1.79%.

Measurements of lactate indicate a slight negative bias. This bias is difficult to detect in the correlation plot, which is presented in Figure 3. Regression analysis of this plot provides a slope of 0.997 ± 0.001 , a y-intercept of -0.1 ± 0.2 mM, and an R-square value of 0.9996. The negative bias is evident, however, from the residual plot

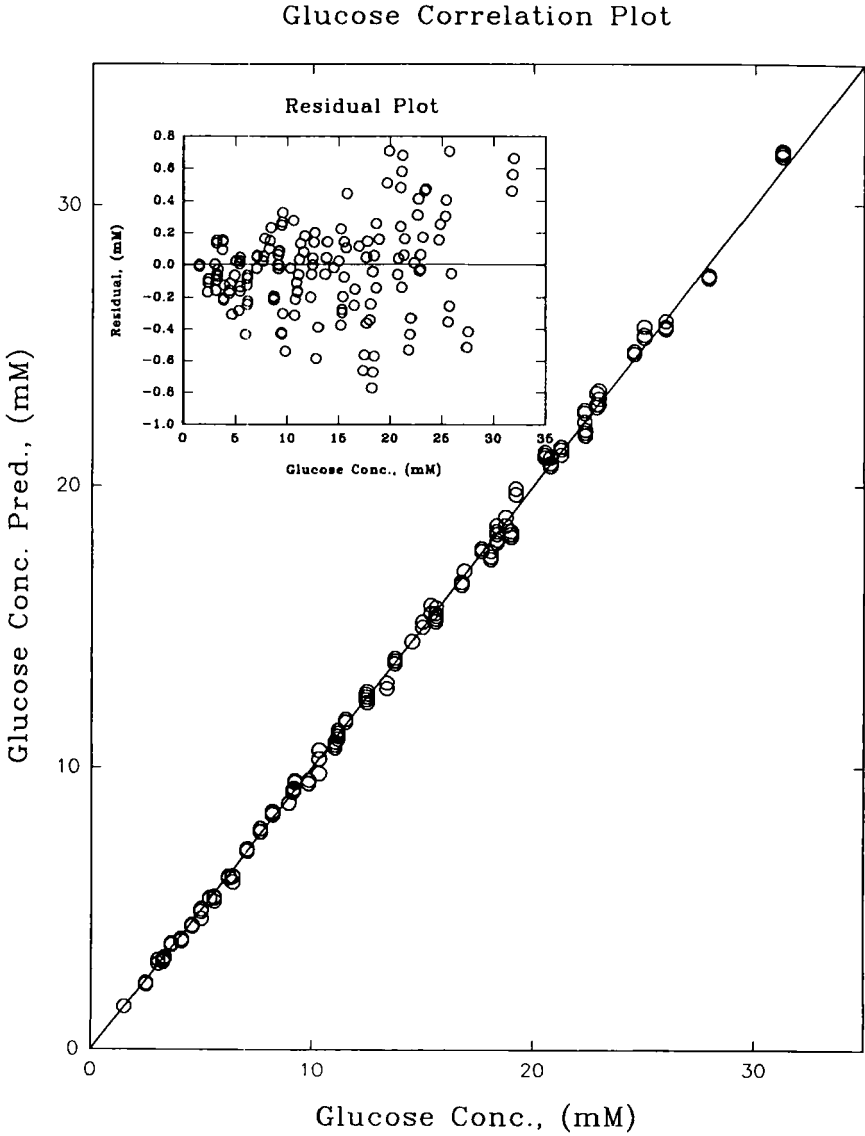


Figure 2. Correlation plot for glucose. Solid line shows the ideal unity line. Inset shows the corresponding residual plot.

TABLE 1

Prediction Ability Over Different Analyte Concentration Ranges

Glucose				Lactate			
Range (mM)	N*	SEP (mM)	MPE (%)	Range (mM)	N*	SEP (mM)	MPE (%)
1 - 5	9	0.13	3.05	0.1 - 1.5	25	0.08	9.71
5 - 10	12	0.20	1.99	1.5 - 5	25	0.16	4.05
10 - 20	23	0.30	1.47	5 - 15	10	0.26	2.36
20 - 30	12	0.38	1.32	15 - 31	15	0.26	0.88
1 - 30	56	0.28	1.79	0.1 - 31	75	0.18	5.10

*Number of observations.

which is presented as an inset in Figure 3. This plot clearly shows an uneven distribution of residuals with 169 of the 224 observations (75%) below zero. The overall mean residual is -0.07 mM. As with the glucose measurement, the SEP and MPE depend on the concentration range tested. Table 1 summarizes the computed values for several, arbitrarily selected, concentration ranges within our lactate data set. The SEP and MPE values for the entire data set are 0.18 mM and 5.10 %, respectively.

Conclusions

Results presented here demonstrate that SEP values for the YSI model 2300 Stat Plus Glucose and Lactate Analyzer are 0.28 and 0.18 mM for glucose and lactate, respectively. No systematic bias was detectable for glucose over the concentration range from 1 to 30

Lactate Correlation Plot

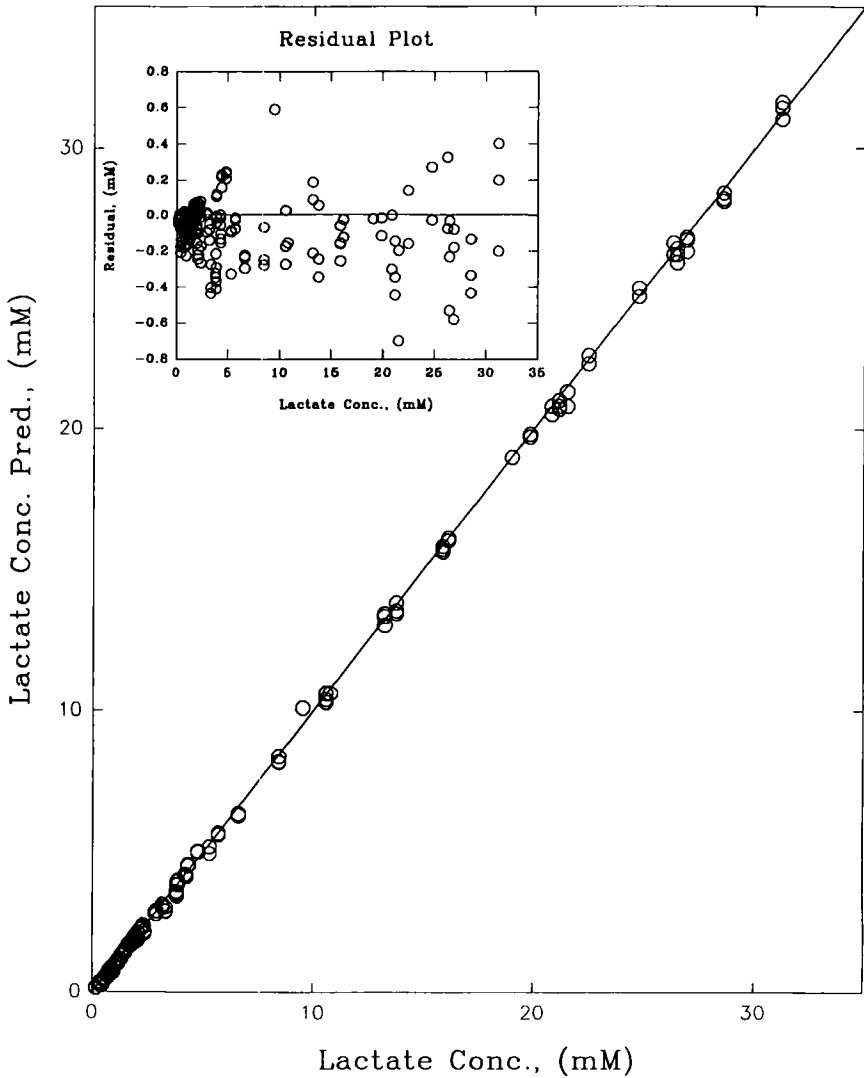


Figure 3. Correlation plot for lactate. Solid line shows the ideal unity line. Inset shows the corresponding residual plot.

mM as long as the instrument is operating properly. A negative bias for glucose was detected initially, however, and this problem was eliminated by performing routine maintenance on the instrument. Periodic accuracy testing is recommended in order to identify instrumental problems. Even with a proper functioning instrument, a slight negative bias was detected for lactate measurements over the concentration range from 0.1 to 30 mM. As a result, the prediction ability for NIR spectroscopic methods for glucose or lactate cannot be lower than 0.28 and 0.18 mM, respectively, if this analyzer is used to supply the required reference information.

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