A Method for Quality Verification of Bio-Optical Measurement System

JUNG-JA KIM[1], JUN-SEOK PARK[2], HUYNH T. HIEU[2] and YONGGWAN WON[1,2]
[1]

Chonnam National University
ICI BDL #202, 300 Yongbong-Dong, Buk-Gu, Gwangju 500-757
KOREA
[2]The School of Electronics and Computer Engineering,
Chonnam National University
ENG BLD #6, 300 Yongbong-Dong, Buk-Gu, Gwangju 500-757
KOREA

Abstract: - In measuring certain biological and chemical information from the human whole blood, several parameters are involved. The measurement parameters for the whole blood are varies from one sample to another, which makes measurement of a biological parameter less consistent through repeated measurements. In this situation, it is very hard to perform a *total quality assurance* for a bio-optical signal acquisition system due to variation over the sample measurements because many types of error can be caused at any step of the measurement procedure. In this paper, we propose a clustering-based measurement for quality assurance for a bio-optical signal acquisition system. We defined '*Discrimination Index*' used as an index for quality verification of the system. We present an experimental result for a measurement system for a bio-optical glucose sensor. For three groups of human blood samples, the experiment showed that our proposed method produced distinct values for two different sample groups, while produced similar values for two similar sample groups. Our proposed method can be also used as a generalized method for reliability verification for a signal acquisition system that measures the samples with parameters that varies from one sample to another.

Key-Words: Bio-optical signal measurement, Clustering, Discrimination index, Bio-sensor, Glucose, Hematocrit, Optical kinetic curve, Quality verification

1 Introduction

There are many methods for detecting or measuring biological or chemical reactions such as electric, electro-chemistry and optics [1]. Most instruments are electronic devices and so must have an electrical signal for an input. One of input signal acquisition method is a measurement of a bio-potential and thus some form of electrode is used between the sample and the instrument. In other cases, a transducer is used to convert some non-electrical parameters or stimulus to an analogous electrical signal proportion to its original parameter.

Bio-sensors, no matter what type of signal acquisition method is applied, sustain many types of errors: insertion, application, characteristic, dynamic and environmental errors [2]. It is natural and generally can not be avoided. Thus, the results of measuring or detecting a parameter of biological or chemical reaction can not be consistent through repeated measurements, and suffer from some degree of variation over the samples.

Depending upon the type of error, the error reduction technology can be different. If the measurement result is governed by the variation caused by instability of bio-materials immobilization, one should place an effort to improve the quality of sensor surface on which the bio-material is fixed, to find a better bonding method for retaining the consistent amount of bio- or chemical material over the bio-sensor surfaces, to control the quality of reagents, etc. Since the errors are generally caused from any step of production process, it is very long and tedious work to reduce the errors.

In these circumstances, it is very complicated to determine weather a measuring equipment produces the precision within the acceptable limitation, since the final measurement value includes the errors from both the bio- or chemical material, bio-sensor device and the equipment itself. We propose, in this paper, a

method to verify the reliability of a measuring equipment, specially a bio-optical signal acquisition system. The fundamental idea is using clustering method.

In the next section, we discuss the motivation of this study, and the definition of measurements with which the reliability of the system will be tested is described in the section 3. Data acquisition system, which is the multi-channel version of the measurement system that should be verified, data acquisition procedure and the data set description are in the section 4. Using the measurement criteria, reliability of a multi-channel glucose measurement system was tested, and its results are provided in the section 5.

2 Motivations

In measuring the level of glucose in the blood, several vital parameters of the blood are involved, such as Po_2, pH, Pco_2, and hematocrit [3]. Some parameters are increasing factors; others may be decreasing factors. Measuring a marker which reflects the level of glucose involves one or more chemical reactions. During the chemical reactions, un-wanted chemical process can be occurred and thus a quantitative measurement is difficult.

As described in [4]-[6], there is a correlation between the level of hematocrit and the value for glucose level obtained by a metering equipment. The effects of low and high hematocrit values could cause critical measurement error [4]. One should be extremely cautious when the patient's hematocrit value changes, particularly if there is a simultaneous change in glucose level [5].

With these facts, determining whether a measuring device is properly functioning is very hard due to variation of the blood samples themselves. For instance, patients with different levels of hematocrit and the same glucose level produce different measured values, which could be critical. Even though one may know there is an error in the measured value, it is hard to differentiate the error caused by the equipment (measuring system) from that by other parameters such as hematocrit level.

To overcome the problems caused by this situation, we proposed a method to verify the reliability of the optical glucose measuring equipments. In other words, our proposed method can test the reliability of the entire procedure for a bio-optical signal acquisition system without separating the error caused by the device (i.e.,

bio-sensor) and equipment (i.e., measuring instrument) from the error caused by the variation of the blood samples (i.e., different level of hematocrit). Since this proposed method evaluates the whole procedure of data acquisition, it is more practical than any method that separately evaluates the device, the equipment and the blood samples.

3 Definitions

Main idea to verify the entire procedure of data acquisition is to evaluate the results of clustering the optical kinetic curve patterns. The kinetic curves from the human blood samples with the same or similar parameters should be in the same cluster [7]. To implement this evaluation method, we define a measurement called 'Discrimination Index' *DI*.

We used fuzzy *k*-means method for generating the clusters [7]. The number of clusters was determined by running for many different values for *k*.

3.1 Cluster Scatterness

The scattering degree of the pattern vectors that compose the *i*-th class is defined as

$$S_i = \sum_{j=1}^{c} \left(\sum_{\mathbf{x} \in D_j^i} \sum_{\mathbf{x}' \in D_j^i} \left\| \mathbf{x} - \mathbf{x}' \right\| \right)_{\big| \mathbf{x} \neq \mathbf{x}'} \qquad (1)$$

where D_i represents the cluster domain of the i-th class, $\mathbf{x}$ and $\mathbf{x}'$ are the pattern vectors of the optical kinetic curve, and c is the number of clusters in the data set of the *i*-th class. Note that if the clusters in the *i*-th class are compact, S_i should have a small value.

3.2 Cluster Distance

Consider that a class is composed of one or more clusters. A between-class cluster distance is defined by the sum of Euclidean distance between the clusters composing the *i*-th class and those composing the *j*-th class. It is the summation of the distance between the centers of the clusters belonging to the *i*-th class and those of *j*-th class, which is formalized as

$$CD_{ij} = \frac{1}{n_i + n_j} \left(\sum_{\mathbf{m}_i \in D^i} \sum_{\mathbf{m}_j \in D^j} \left\| \mathbf{m}_i - \mathbf{m}_j \right\| \right)_{\big| D^i = D^j} \qquad (2)$$

where m_i is the center of a cluster that belongs to the *i*-th class, and n_i is the number of clusters in the *i*-th class. Note that if the *i*-th class and the *j*-th class are

well-separated from each other, then CD_{ij} should have a relatively larger value.

3.3 Discrimination Index

We defined a measurement which represents an index that shows how well the *i*-th class can be discriminated from the *j*-th class, called Discrimination Index $DI_{i \rightarrow j}$ and described as

$$DI_{i \rightarrow j} = \frac{CD_{ij}}{S_i} \qquad (3)$$

Note that $DI_{i \rightarrow j} \neq DI_{j \rightarrow i}$ since $CD_{ij} = CD_{ji}$ and $S_i \neq S_j$. Also, the larger value means that the *i*-th class is easier to classify from the *j*-th class.

4 Experiments on Verification

4.1 Bio-Optical Signal Acquisition System

We designed and implemented a measuring equipment. It acquires the optical signal which is a light reflectance information from the glucose bio-sensor along the time, which is called *%R kinetic curve*. The system is composed of the following functional blocks:

- *Light emission*: generates specific light wave(s)
- *Light absorption*: accepts the light reflected from the surface of the bio-sensor, and transforms the light signal into electrical signal
- *Bio-sensor holder*: a part that has a structure to properly hold the optical bio-sensor.
- *A/D conversion*: converts the analog electrical signal into digital signal

- *MCU(Main Control Unit)*: performs control and management of the system. Main computing unit and memory.
- *Signal processing*: general signal processing unit.
- *Display*: shows information and values

The system which has 6-channel optical probes is shown in Fig 1. The large box is the main station which has the control unit, signal conversion, signal processing, and computer interface. The six small boxes are the optical signal acquisition probe which has emission, absorption and sensor holder. Note that each probe can be a single optical signal acquisition system.
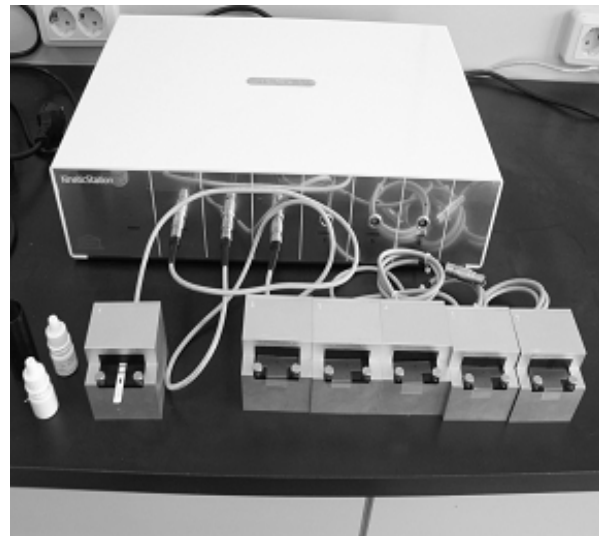

Fig. 1   Optical kinetic station which measures light reflectance signal along the time

4.2 Data Acquisition

Quantitative measurement of glucose in whole blood with an optical bio-sensor begins when a drop of blood is supplied on the porous membrane on the top of the strip. The membrane separates the erythrocyte from the plasma in the blood sample. The plasma diffuses into the reagent layer, and some chemical reactions with enzymes are followed, which results in change of the dye in the strip into a blue color. The intensity of the color developed is proportional to the glucose concentration in blood and is transformed into glucose reading by a measuring equipment such as hand-held glucose meter.
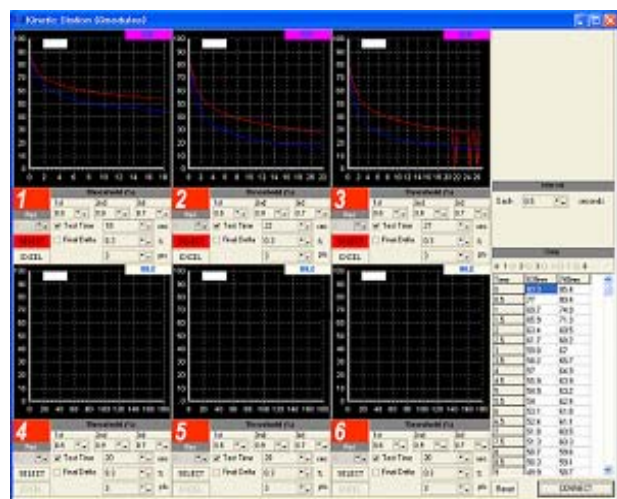

Fig. 2   Data acquisition software which acquires %R kinetic data from the 6 optical probes

With the bio-optical signal acquisition system described in the section 4.1, we acquired %R kinetic curve data for 20 second with the discrete interval of 1 second. Optical glucose bio-sensor used for this study can be anyone available in the commercial market.
We developed a software to control the multi-channel acquisition system. Using this software, %R kinetic data from 6 optical probes are independently collected at a time. The GUI (Graphical User Interface) of the software is shown in Fig. 2.

Collected data can be saved in to a file, and data from each probe is a 21-dimensional pattern vector since the value at time 0 is included.

4.3 Data Set Description

For this study, 3 different types of blood samples were collected as shown in Table 1. Group 2 and Group3 are similar by having the samples of high viscosity and high level of hematocrit, while Group1 had the samples of low viscosity and low hematocrit level. Thus, Group1 should be easily separable from either Group2 or Group3.

Table 1. Statistics of data samples

	Viscosity	H. L	N. S.
Group1	Low	Low	30
Group2	High	High	30
Group3	High	High	30

Note) H.L (Hematocrit level) N.S(Number of samples)

5　Results and Conclusion

In 21-dimensional pattern space, Group1 should be separable from Group2 and Group3, while Group2 and Group3 are hard to separable from another. In terms of Discrimination Index, $DI_{2\rightarrow3}$ and $DI_{3\rightarrow2}$ should be low relative to other values $DI_{1\rightarrow2}$, $DI_{1\rightarrow3}$, $DI_{2\rightarrow1}$, and $DI_{3\rightarrow1}$, as defined in the equation (3). For the data set we used, the values of *Discrimination Index* are presented in Table 2.

There are two facts: 1) optical glucose bio-sensors we used are obtained from the commercial market, and 2) viscosity and hematocrit level were measured by high precision devices. Those two facts supports the argument that errors from the sensor devices and measurement of viscosity and hematocrit level are small enough to be acceptable. Based on these facts, we can conclude that the measuring

equipment described in the section 4.1 is working properly. This is a simple method for verification of a measuring equipment.

Table 2. Discrimination Index for the three groups

	j / i	1	2	3
Discrimination Index $DI_{i\rightarrow j}$	1	-	3.017	2.938
	2	3.324	-	0.894
	3	3.002	0.903	-

Although we used the bio-sensors in good quality, any bio-sensors that need a quality assurance can be used for verification with a quality-proven measuring equipment. Also, our proposed method can be applied to integrative quality verification from the bio-sensor device to the measuring equipment.

References:
[1] R. S. Cobbold, *Transducers for Biomedical Measurements,* Wiley, 1974
[2] J. J. Carr and J. M Brown, *Introduction to Biomedical Equipment Technology*, 3rd Ed, Prentice Hall, 1998
[3] J. Pickup, L. McCartney, O. Rolinskey and D. Birch, In vivo glucose sensing for diabetes management: progress towards non-invasive monitoring, *BMJ,* Vol. 319, Issue 7220, November 1999.
[4] Richard F. Louie et al, Point-of-Care Glucose Testing: Effect of Critical Care Variables, Influence of Reference Instruments, and a Modular Glucose Meter Design, *Arch. Pathol. Lab. Med.*, Vol 124, Feb. 2000, pp. 257-266
[5] Tang et al, Effects of Different Hematocrit Levels on Glucose Measurements with Handheld Meters for Point-of-Care Testing, *Arch. Pathol. Lab. Med.*, Vol. 124, Aug. 2000, pp. 1135-1140
[6] A. Brouwers, D. Bernard, and M. Langlois, Clinical and Analytical Performance of the

Accu-Chek Inform Point-of-Care Glucose Meter, *Point of Care: The Journal of Near-Patient Testing & Technology*. Vol. 4, No. 1, March 2005, pp. 36-40

[7] R. Duda, P. Hart and D. Stork, *Pattern Classification*, 2nd Ed, Wiley Interscience, 2001