Doctoral Dissertation (Shinshu University)

Study on noninvasive blood glucose measurement using optical fiber sensor and its application

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1.1 Background

According to the Ministry of Health, Labor and Welfare's statistics, “National Medical Expenditure,” medical expenses is increasing. In FY2017, medical expenses will fall to about 8% of GDP, and the national profit ratio will exceed 10% [1]. One cause is an aging society. It is now a global issue as well as Japan, and there are concerns about the end of the sustainable development of social systems. In the future, aging may progress further [2], it is not avoid to the increase of medical expenditure invoke more bigger problems. In such circumstance, people's health awareness is increasing, as well.

According to the statistics of 2014, three groups of 20-39 years old, 40-64 years old, 65 years old and over, all groups think that they need “information about the body" and "information about medical / medical facilities." Those opinion of the groups dominate over half of them [2]. It is also a problem such as the separation of life span and healthy life span, the

demand for being healthy is getting to increase.

I would also like to pay attention to the current state of diabetes. Diabetes is one of the heavy special illness, diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Referring the statements of WHO declared, the person with diabetes has been spreading from 108 million in 1980 to 422 million in 2014 [3]. There is also estimation which says the number increase to 500 million in 2030. And, the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 [4]. Almost half of all deaths attributable to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016. This serious illness, diabetes is treated specially even in Japan, medical institution can demand special fee for facing diabetes as "Special illness managing fee." This means that the Minister of Health, Labor and Welfare admitted that "carefully scheduled treating is needed for diabetes", in other words, he is insisting that the diabetes need daily blood glucose level managing. Because blood glucose level is easily fluctuating by normal meal, activity, and condition of mental, blood glucose should be measured several times per day, not only hospital, but also house. However, the instruments for measurement blood glucose level in house; Self-monitoring blood glucose level (SMBG) has a

lot of problems. Firstly, those are an invasive type instruments which need blood for sampling. In the case of the person with diabetes in the hospital, they need pricking needle in the morning, after breakfast, after lunch, after dinner, before sleeping, for example. There will be a stress, pain, and risk of blood infection, every single time. Secondly, those instruments require a lot of disposable parts, running cost must be increasing. Sometimes the cost reaches hundreds of thousand yen per year. Thirdly, current food circumstance is one of reason which has tendency to increase blood glucose level. Now days, various foods are added purified sugar or artificial sugar. In the case of high fructose corn syrup, it can be started to absorb into body with a few minutes, in contrast to 50 minutes, in the case of rice. Then, the blood glucose level is increased drastically by directly entering glucose into the body. The rapid increase in blood glucose level caused by this method shows a value that greatly exceeds the reference value in a short time that is not captured by the conventional measurement frequency. We are in the environment which need more high frequency of blood glucose level measurement. Finally, diabetes has a congenital type. It is quite big problem, in such situation, protectors have to prick needle to their own child and bleed, several times, every day. Nobody can guess that their thought and feelings in this case. It is obvious that we should not overlook this situation. As here

stated before, current instruments include a lot of problems, genuine non-invasive type blood glucose measurement devices have been strongly demanded for long time. This increase has led to strong needs for a rapid, painless, risk-free self-blood-glucose measurement method [5]–[7].

1.2 Current circumstance and demand of vital sign monitor

Aging society is now problem of world. That is quite big problem for all developed countries, like it in Japan, leads various serious problems, increasing of patients, increase in a burden of treatment cost to a patient and governments, lack of insurance budget. Even in nursing facility, they insist the lack of worker and human resources, they are in serious condition that they have to invite worker from the over sea. We are in such social condition and state, our health consciousness is quite high level that appeared never.

Healthcare orientated vital sign monitoring can be one of powerful solution. By monitoring various vital signs, it can give the notification in early stage of illness, and help to treat in advance. That leads to the providing the prevention disease. The idea of vital sign monitoring is getting a lot of

attention from the companies to improve the productivity with aspect of health management or health investment [8]. The concept of brand "health management brand" is imported, the tendency of health management is getting to appear among the companies. As well as the individual stages, developing the electric devices help among the popularization of health monitoring for the people, now most of the smartphone are installed health managing applications. Some statistic says that the rate of utilization grow to double with latest 2 years, 54 percent of those user answer that they use application beyond 5 days in one week [9]. As well, the wearable devices which was used for limited few user or industries, now change into healthcare purpose for individual person. Addition, main manufacturer is also gradually changing, from IT company to fashion luxury brand, it is clear that the health care wellness is spreading into various industry field. Moreover, because healthcare monitoring desire to be all-time working system, there has been big development of wearable devices. Taking these tendencies, the product which target vital sign measurement is appearing in smart textile field. Like in Hitoe [10], there already some product are available on market.

As stated before, various product has been developing with various field, however, the devices which measure vital sign is mainly big and

specialized to one function. Furthermore, most of this device are only able to detect the pulse rate, breathing rate. It is because those devices depend on the "conductive fiber" or "Photo electric plethysmogram wave meter" as a core technique for measurement. The devices which use Photo electric plethysmogram wave meter are not possible to detect blood pressure nor blood glucose levels, and weak against the water. Addition, kind of those products, part of activity tracker has been suspected with its reliability.

On the other hands, our research group has been proposing the vital sign monitoring using optical fiber sensor. This is the measurement based on the fiber-shaped strain sensor; Fiber Bragg Grating (FBG) sensor, different with former sensors, it is possible to detect the various vital sign using just single FBG sensor. It is proud of quite high sensitivity and non-invasively, taking advantage of fiber-shape, it is possible to be loaded into various products. Excellent compatibility with knitting, making it a promising candidate for the creation of smart textiles with multi-vital sign measurement function [11].

1.3 Present situation of Self-Monitoring Blood Glucose

As stated before, there has been a lot of studies and strong need for non-invasive blood glucose measurement. Research and development for measurement methods based on spectroscopy began in the 1970s. It is well known that attenuated total reflectance [12] or near-infrared diffuse reflectance spectroscopy [13] had been applied to realize non-invasive blood glucose monitoring, mainly for diabetic patients. Since then, various developments have been made. A microwave measurement system has been proposed to monitor blood glucose non-invasively. Microwave sensor technologies were studied based on the frequency dependence of amplitude with the subject's thumb being placed at a fixed point on an open-terminated spiral-shaped micro strip line [14], [15]. In the analysis method of calculating the blood glucose level, a method of calculating blood glucose level with high accuracy by applying artificial neural network (ANN) [16], partial least squares regression (PLSR) [17], and the like has been studied. In the measurement method using light, a method of calculating blood glucose level by Raman spectroscopy has been reported [18], [19]. In report of Spegazzini, Raman spectra were recorded at regular 5 min intervals from the

forearms of these volunteers, blood glucose concentrations were calculated by using the improved concentration independent calibration (iCONIC) approach with Raman spectra [19]. However, since these are methods of irradiating light on the body, there is a danger that the measurement accuracy of the blood glucose level will be influenced by the surface condition and body temperature of the skin of the subject. Currently, half-invasive type measurement devices or “Continuous Glucose Monitoring (CGM)” solutions, such as the Freestyle Libre (Abbott co. ltd) and iPro2 (Medtronic co. ltd), have been released to market. However, these devices are limited to measure glucose in intervals of 6–15 minutes, only. Those devices can not follow the drastic changes in blood glucose level, such as glucose spikes after meals in daily life, at this measurement frequency. Ultimately, these devices are not truly non-invasive, as they cannot measure blood glucose accurately without pricking sensors to the skin. Genuine non-invasive and rapid measuring method which don't need bleeding has been strongly needed.

1.4 The purpose of research

In order to produce multiple vital sign monitoring device, this research set the ultimate goal that creating the wearable, multiple vital sign monitoring device. Along this thought, this dissertation has 2 aspects. The former part of dissertation, chapter 2 and 3 state the considering about adding the blood glucose measurement function to the FBG sensor system. This function works by the method to pick up the information of blood glucose level from pulse wave signal got from optical fiber-type strain sensor system which is FBG sensor system. Chapter 2 and 3 adopt each different method to analyze. Adding the blood glucose measurement function lead to making possibility that helping potential 500 million diabetic persons. We can say that there are large scale of merit and advantages and this theme is worth to struggle.

On the other hands, latter part of dissertation describes the way to practical use of the FBG sensor system. Chapter 4 explain about trial of introducing an FBG sensor system in a sleeping environment. Facing at the sleeping condition measurement, method is required to being non-intrusive and non-binding one for comfortable sleep. Therefore, this chapter report the how to measure vital sign from attaching FBG sensor system on the bedding,

not on the human body. Next, chapter 5 describes a research on mounting FBG sensors on human-shape robots to construct a system that actively performs vital sign measurements. As a development result, this human-shaped robot was able to measure the pulse rate, breathing rate, and blood pressure.

Chapter 2
Extraction of blood glucose information contained in pulse wave signal

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2.1 Introduction

The technique by analyzing pulse wave has been presented since a long time ago. Especially, the "acceleration of pulse waveform" which is secondly differential of the signal from Photo electric plethysmogram wave meter has been studied relationship between age, blood vessel, and various diseases [20]. The information from there are not little, movements of heart, breathing rate estimation, indicator for heart disease or arteriosclerosis was target.

In recent years, photoelectric plethysmographs have become widespread and it has become familiar to obtain information from pulse wave shapes. It is used in various ways such as blood vessel age measurement devices (Figure 2-1) and wrist-watch type heart rate monitoring. In many cases, the degree of blood flow is estimated from the

amount of light absorbed by hemoglobin flowing into blood using green visible light or infrared light. Although taking advantage of the non-invasive nature of optical measurement, various problems remain, such as skin color, water effects, and measurement reliability. Above all, measurable items are limited to pulse, respiration, and momentum. That's why we have been focused on the FBG sensor system. FBG sensor is a highly sensitive strain sensor, by attaching the FBG sensor on the human body, it can measure the human pulse wave with high-resolution. A pulse wave is a measurement of a pressure change or a volume change of a peripheral blood vessel propagated by a heartbeat. When the heart contracts and blood is ejected from the left ventricle into the aorta, there is a change in the aortic pressure. Furthermore, this pressure fluctuation is propagated to the peripheral artery, and it propagates as strain to the body surface on the radial artery. The FBG sensor measures strain change due to pressure fluctuation. The signal of pulse wave measured by the FBG sensor is defined as a “pulse wave signal.” This recorded pulse wave signal has time in horizontal axis and amount of change of Bragg wavelength in vertical axis, which can be observed visually only the number of pulse waves. owing to the FBG sensor's high sensitivity, it has been gradually founded the signal include the information of various vital signs. By analyze and setting the pulse wave signal as an explanatory

variables and setting the breathing rate, stress loading level or blood pressure as reference variable, it is possible to calculate those vital signs from measured pulse wave [21], [22]. The interval between one period of each pulse peak to the next peak has slightly different with next interval, focusing on this, breathing rate and stress loading can be calculated. On the other hands, in case of blood pressure, the shape of each pulse wave is changed depend on the blood pressure values. This acceleration plethysmogram is said that it is an indicator for arteriosclerosis and condition of dosing, and be suggested that contains a lot of vital information. Focusing on the details of signal and analyzing the corresponding between blood pressure values and pulse by multivariate analysis, blood pressure can be calculated. Like written in before, acceleration plethysmogram is affected by the condition of arteriosclerosis, dosing, aging and so on, in other words, acceleration plethysmogram may include the information of blood ingredients and tissue around blood vessel. Thereupon, extracting the information of blood ingredients is considered, blood glucose level attracted attention. Recent years, the demands for monitoring blood glucose level is increasing along the increasing of diabetes. Addition, the blood glucose level is the level of the glucose in blood. It is can be thought that change of blood glucose level

might bring the change of viscosity, and affect the shape of pulse wave form.

Therefore, this chapter states whether the pulse wave signal measured by FBG sensor system include the information of blood glucose level or not. If it is possible to take up the blood glucose information from the signal, FBG sensor's high non-invasiveness and convenience will be great advantage of the blood glucose measurement instrument. In this measurement trial, the FBG sensor is installed at the radial artery of the wrist, and a pulse wave signal is measured. The method is safe for the human body and does not involve the collection of blood. Since the blood glucose level is the glucose concentration in the blood, the blood flow will change owing to blood glucose level fluctuation and affect the pulse wave signal. If the FBG sensor can measure the pulse wave signal fluctuation, then the blood glucose level can be measured. Herein, the result of calculating the blood glucose level from the pulse wave signal measured using the FBG sensor and the prospect of non-invasive blood glucose level measurement by this method are described.

Figure 2-1 blood vessel age measurement device

2.2 Measurement principle and method

2.2.1 FBG Sensor System

In this experiment, an FBG sensor system (PF25-S01: Nagano Keiki, Inc., Tokyo, Japan) was used [23]. This sensor system consists of an interrogator and an optical fiber. Figure 2-2 shows the photo and schematic diagram of the FBG sensor system. Broadband near-infrared (NIR) light with a wavelength range of 1525–1575 nm propagates through the optical fiber. Light reaches FBG sensor 1 through the optical circulator. The FBG sensor is a diffraction grating, in which the

refractive index of the core of the optical fiber varies at equal intervals and has an optical filter function. In this diffraction grating, only a specific wavelength (Bragg wavelength) of NIR light from the light source is reflected, according to Equation (1), depending on the diffraction-grating spacing:

$$\lambda_{Bragg} = 2n_{eff}\Lambda \quad (1)$$

where λ_{Bragg} is the Bragg wavelength, Λ is the diffraction-grating spacing, and n_{eff} is the refractive index inside the core. When strain is applied to the sensor section, the diffraction-grating interval changes, because of which the Bragg wavelength also changes. This Bragg wavelength shift is measured by a Mach-Zehnder interferometer-type detection mechanism. The reflection light interferes in an interferometer, in which the optical path difference is set to 3.3 mm. A beam splitter splits the light into three components having phases that differ from each other by $2\pi/3$ radians. The three phases are detected by wavelength division multiplexing. Three pairs of detectors detect the phase shifts of sensors 0 and 1, as shown in Figure 2-2. The signal for temperature correction of the measurement environment is measured by the FBG sensor 0 which showed in Figure 2-2. The phase resolution depends on the sampling frequency, which is 10 kHz. The FBG sensor measuring

the pulse wave signal is shifted by 1.2 pm, with a strain of 1 με, and the measurement sensitivity is ±0.1 pm [24]. Using this system, the pulse wave signal was measured as a continuous signal showing a wavelength shift with respect to the time axis. The specification summarized in

Table 2-1 Specification of FBG sensor system

Light Source	Type	Amplified Spontaneous Emission
	Power	30 mW
	Wavelength range	1525–1575 nm
FBG Sensor	Length	10 mm
	Bragg wavelength	1550 ± 0.5 nm
	Wavelength resolution	0.1 pm
	Strain resolution	0.08 μm
Detector	Type	InGaAs PIN PD
	Wavelength range	900–1650 nm

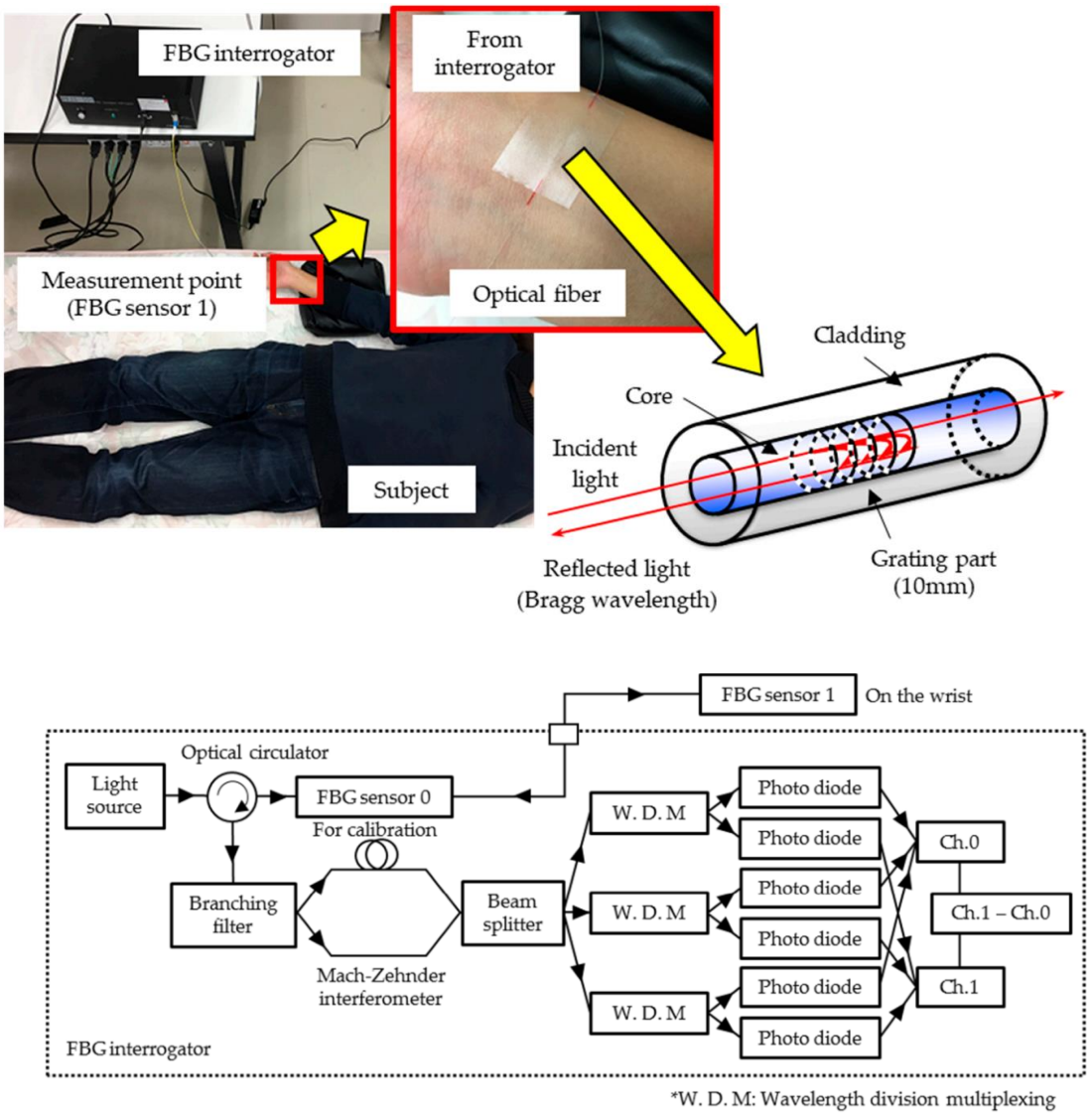


Figure 2-2 Photo and schematic diagram

of the fiber Bragg grating (FBG) sensor system

Figure 2-3 Representative photograph of a subject during pulse wave measurement.

2.2.2 Pulse Wave Signal and Blood Glucose Level Measurement

Four subjects, who are all healthy males in their 20s, participated in the study. To measure the pulse wave signals, the FBG sensor was attached to the subject's skin at the radial artery with a medical adhesive tape. In this measurement method, the strain of the artery that has propagated to the body surface is measured, so the calculated accuracy of the vital sign measurement is not affected by the

color of the skin of the subject. Figure 2-3 shows the appearance of a typical pulse wave measurement in this study. The subject was in the supine position, and the wrist was kept as high as the heart. The measurement was performed for 20 s. For avoid the effect of body movements, blood glucose level is measured first, immediately after, pulse wave is measured.

Blood glucose was measured using an invasive blood glucose sensor, AntsenseIII (HORIBA Co., Ltd., Kyoto, Japan) or FreeStyle Precision Exceed H (Abbott Japan Co., Ltd., Osaka, Japan). This blood glucose level is used as the reference blood glucose when the pulse wave signal is measured. Immediately after measure blood glucose level, FBG sensor system measure pulse wave. While FBG sensor system running, blood glucose level is showed. The relative uncertainty of the invasive blood glucose values in this reference method is 3.3–6.5%, when the glucose concentration is in the range of 90–220 mg/dL. In this experiment, the measurements were performed 20 times when the subject was in the fasting state, and they were performed another 40 times several hours after the subject had a meal. In the blood glucose level measurement experiments, blood glucose levels usually change with the oral glucose tolerance test (OGTT). In order to measure the

blood glucose level, which is close to the usual life, we chose a method to change the blood glucose level by meal. Figure 2-4 shows the time-series change in the blood glucose level of subject D. All of the subjects gave informed consent before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shinshu University (No.3202, Verification clinical trial with wearable vital sign measurement system.).

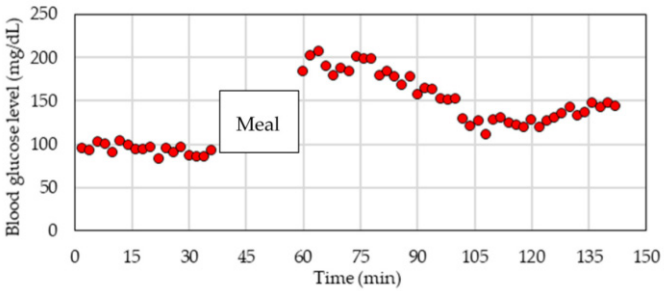


Figure 2-4 The time-series change in the blood glucose level (subject D).

2.2.3 Blood Glucose Level Calculation Method

The pulse wave signal was filtered by a bandpass filter having a pass band of 0.5–5 Hz, and the signal was processed in the first differential. To calculate the blood glucose level from the pulse wave

signal, the following four signal processing steps are necessary.

1. Division of the measured pulse wave signal at each peak by a 1-pulse pulse wave.
2. Averaging of a plurality of divided 1-pulse pulse wave signals.
3. Normalization of the vertical axis (wavelength shift) of the 1-pulse pulse wave.
4. Normalization of the horizontal axis (measurement time) of the 1-pulse pulse wave.

“1-pulse pulse wave” is a signal that is divided at the peak of a pulse wave and indicates a pulse wave signal in single beat of the heart. These processes are important for canceling fluctuations in the 1-pulse pulse wave signal measurement caused by pulse rate and respiration, as well as fluctuations due to the pressure of attachment the FBG sensor to the human body. For the pulse wave division, the peak due to the beat of the heart was selected. That is usually biggest peak in one period.

In the normalization of the wavelength shift in one pulse wave signal, the first peak value is set to “1”, and the first valley value is set to “0”. The measurement time of the 1-pulse pulse wave was normalized using two methods. The first is normalization with the shortest measurement time (shortest-time-cut process). In this

method, the measurement time is normalized by the shortest measurement time (approximately 0.7 s in this experiment) among the divided 1-pulse pulse wave signals. The signal at the back of the 1-pulse pulse wave is discarded, resulting in a reduction of the information in the pulse wave signal. For example, when the measurement time of the 1-pulse pulse wave signal is 0.8 s and the normalized time is 0.7 s, then the signal at 0.7–0.8 s is discarded. This procedure described in Figure 2-5.

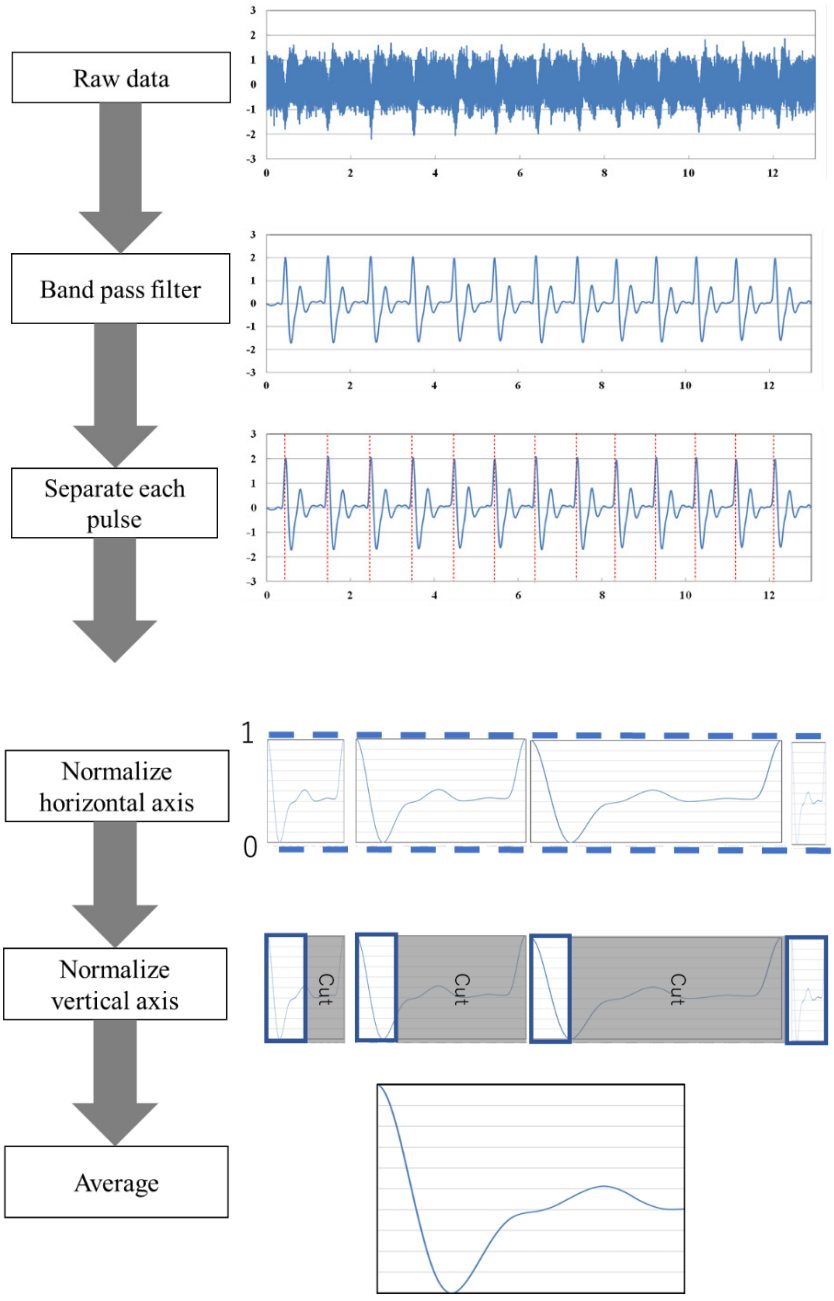


Figure 2-5 Schematic flow of the pulse wave processing (shortest-time-cut process)

The second normalization method for the measurement time is to normalize all 1-pulse pulse wave signals to 1 s (1-s-normalization process). First, the measurement time is multiplied by an arbitrary constant, so that it is 1 s for the measured 1-pulse pulse wave. Next, a new point is created (linear interpolation) on a straight line connecting the nearest two points from 0.1 ms, and a similar calculation procedure is followed at the points of 0.2 ms, 0.3 ms, and so on to construct the 1-pulse pulse wave signal at 10,000 points within 1 s. By applying this normalization method for all 1-pulse pulse wave signals, all of the pulse wave signals are normalized to 1 s. This procedure described in Figure 2-8.

Using these signal-processed pulse wave signals and the reference blood glucose level, a calibration curve for calculating the blood glucose level is constructed by Partial Least Square Regression (PLSR), which is a multi-variate analysis method. Since the reference blood glucose level (measured by the invasive blood glucose meter) has a measurement error, PLSR is suitable. Pulse wave signals were used as the explanatory variables, and the blood glucose levels, as measured by the invasive method, were used as the objective variables. Principle component analysis was performed for the pulse waves, and a feature

vector called the PLS factor was extracted. In PLSR analysis, the objective variables (blood glucose levels) are expressed by a linear combination of the latent PLS factor of the explanatory variables (pulse waves). The residuals were used as the variables of the new model set for the next extraction step until the predicted residues of the objective values reach their minima [25]. The optimal numbers of PLS factors were tested statistically at a 5% significance level. The model set with the calculated optimum number of factors is used as the calibration curve for calculating the blood glucose level. In the validation of the calibration curve, pulse waves that were not used in the calibration were substituted to calculate the predicted blood glucose levels. The standard deviation of the error between this predicted blood glucose level and reference blood glucose level is the standard error of prediction (SEP).

2.2.4 Standard Error

For additional evaluation of our technique, we calculated the standard errors for both the calibration model, and the validation results. The standard error of calibration (SEC) characterizes the error between the reference glucose level and the estimated glucose level used in

constructing the calibration curve. Similarly, the standard error of prediction (SEP) characterizes the error between the reference value and the estimate used to validate the calibration curve. These parameters are calculated as below:

$$\text{SEC} = \sqrt{\frac{\sum(d_i - \overline{d})^2}{\text{n-k}}} \quad (1)$$

$$\text{SEP} = \sqrt{\frac{\sum(d_i - \overline{d})^2}{n}} \quad (2)$$

where di is the predicted value, $\overline{d}$ *is the average of reference values, n is the number of reference materials, and k is the number of unknown factors.*

2.2.5 Error Grid Analysis (EGA)

In addition, error grid analysis (EGA) [26] was used for validating the calculation of blood glucose using this measurement method. EGA was originally used by Clark [27] to verify the clinical efficacy of blood glucose sensors. A scatter diagram with the reference blood glucose level on the horizontal axis and the blood glucose level calculated with the developed measurement method on the vertical axis is divided into five zones, labeled A–E. EGA can verify the clinical efficacy in zones A and B, but not in zones D and E. We examine the

proposed measurement method from the results of SEP and EGA.

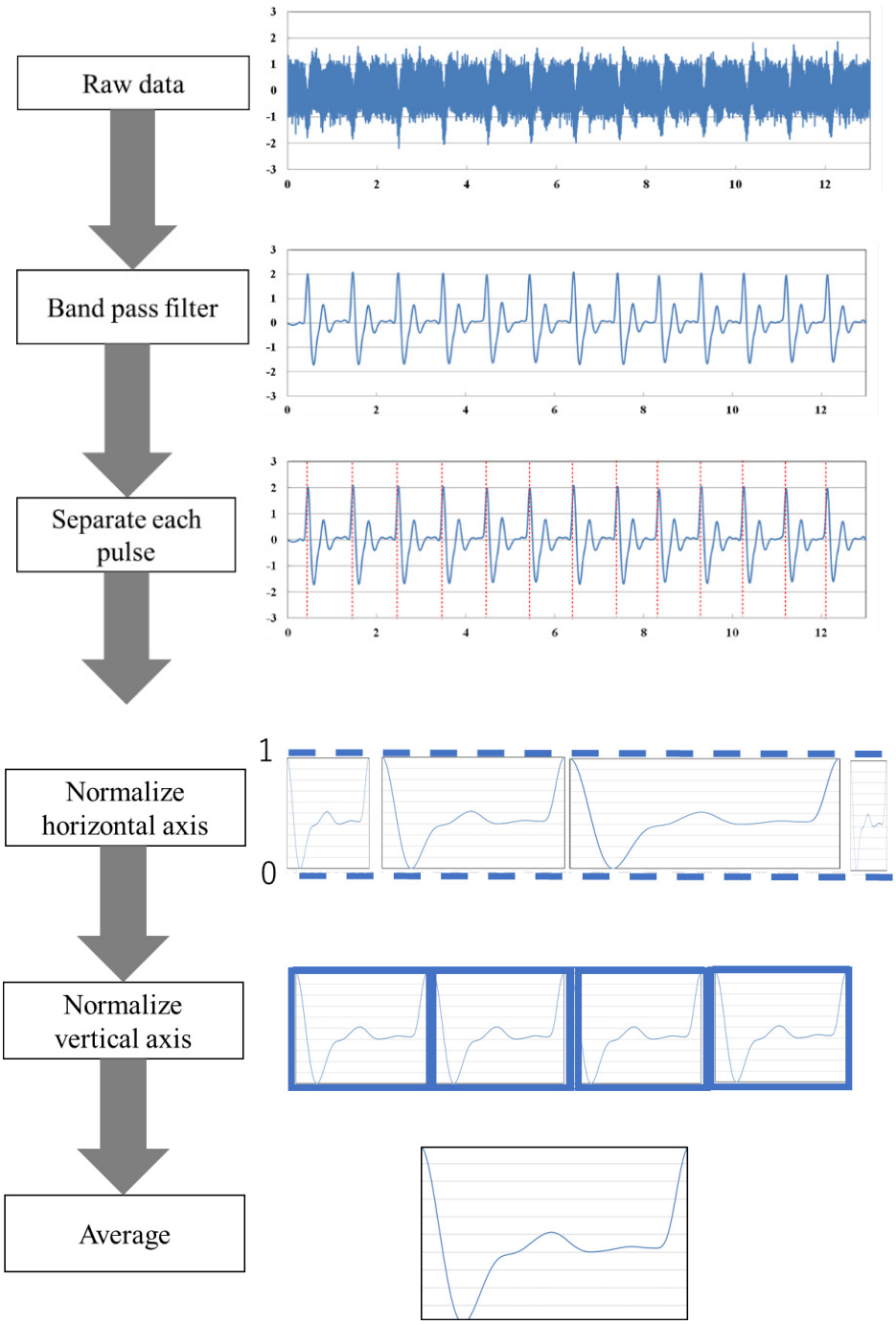


Figure 2-6 Schematic flow of the pulse wave processing (1-s-normalization process)

2.3 Experimental Results and Discussion

2.3.1 Reference Blood Glucose Levels and Pulse Wave Signal of Each Subject

The pulse wave signal and reference blood glucose level were measured 60 times for each subject. The calibration curve for calculating the blood glucose level was constructed with 50 measurements (calibration data set), and the blood glucose level calculation was verified using the remaining 10 measurements (validation data set). This combination had been used in non-invasive blood glucose level measurement with near infrared spectroscopy [28].

Table 2-2 presents the calibration and validation data sets of the reference blood glucose level of each subject. When each subject had meals while being measured, blood glucose levels fluctuated from over 87 (subject C) to 139 (subject B) mg/dL.

Figure 2-7 shows a pulse wave signal subjected to a first-derivative process in addition to a 0.5–5Hz band pass filter, as well as a general acceleration plethysmogram. The acceleration plethysmogram has five peaks labeled A-E corresponding to the beating of the heart [29], [30]. The measured pulse wave signal is very similar to the acceleration

plethysmogram. Therefore, the signal measured by the FBG sensor system is a pulse wave signal including the information of blood flow from the heart.

Table 2-2 Reference blood glucose data set.

Subject (Gender)	Number of Measurements	Blood Glucose Level (mg/dL)		
		Maximum	Minimum	Average
Calibration Data Set				
A (male)	50	178	80	119
B (male)	50	232	93	143
C (male)	50	176	89	127
D (male)	50	207	83	138
Validation Data Set				
A (male)	10	153	82	113
B (male)	10	188	97	138
C (male)	10	164	89	115
D (male)	10	202	85	129

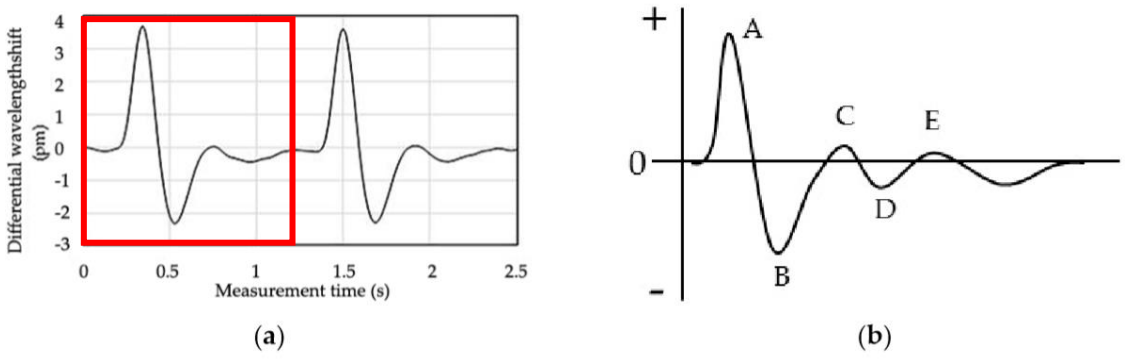
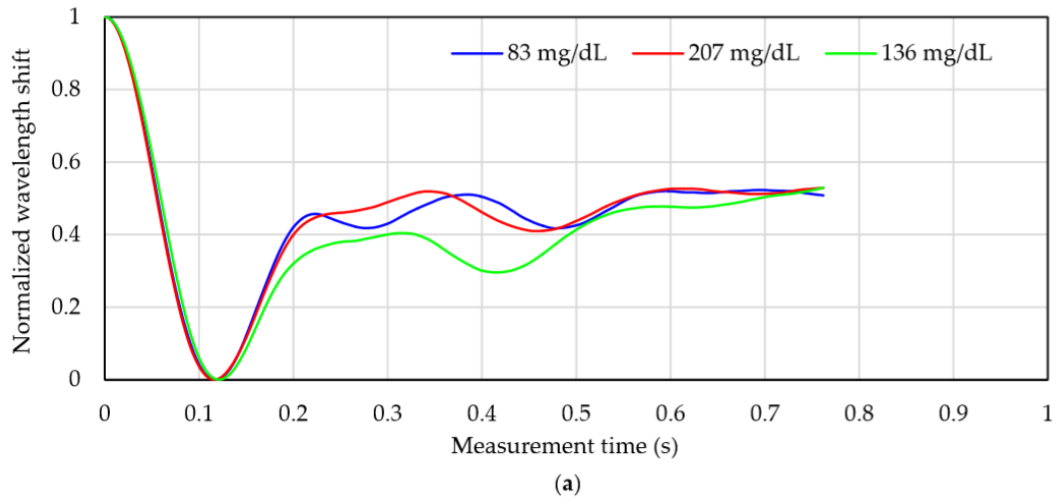
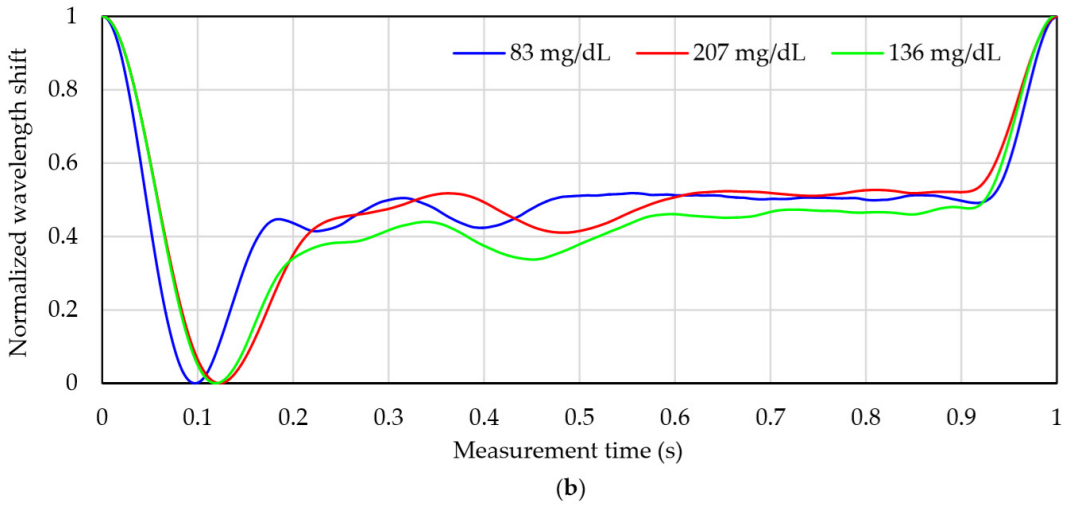


Figure 2-7 Measured pulse wave signal and basic acceleration plethysmogram. (a) Pulse wave signal measured with the FBG sensor; (b) Acceleration plethysmogram.

Figure 2-8 shows the processing of the pulse wave signals for subject D with the two signal processing methods. The pulse wave signals are measured when the subject's blood glucose concentration was maximum, minimum, and around the average value. In Figure 2-8a, the shortest time was 0.76 s; therefore, the pulse wave signal was cut at that time. Depending on the blood glucose level, the shape of the pulse wave signal is different at 0.2–0.6 s for each subject. In shortest-time-cut processing (Figure 2-8a), the measurement time points selected to be "0" for normalization are almost the same (around 0.12 s), but this measurement time point is different in the 1-s-normalization process. Therefore, in the 1-s-normalization process, a large difference appears in the slope of the peak at 0–0.1, 0.1–0.2, and 0.9–1 s. The shape of the acceleration plethysmogram depends on the blood flow and the hardness of the blood vessel. Therefore, since the glucose concentration in the blood flow varies depending on the blood glucose level, it is conceivable that the pulse wave shape is affected by the glucose concentration. The blood glucose level will be calculated by measuring the shape change of this pulse wave signal.



(a)



(b)

Figure 2-8 Pulse wave signal in each signal processing method. (a) Pulse wave signals in the shortest-time-cut process. (Blood glucose level, Min: 83 mg/dL, Max: 207 mg/dL, Ave.: 136 mg/dL). (b) Pulse wave signals in the 1-s-normalization process. (Blood glucose level, Min: 83 mg/dL, Max: 207 mg/dL.

2.3.2 Blood Glucose Level Calculated by Calibration Curve

Since the blood flow changes with the glucose concentration, the blood glucose level is calculated from the calibration curve. The calibration curve is constructed from pulse wave signals that are subjected to the two signal processing methods, as described in section 2.2.3

Figure 2-9 show the calibration curves, blood glucose level calculation, and EGA results for each subject in shortest-time-cut process. show the calibration curves, blood glucose level calculation, and EGA results for each subject in shortest-time-cut process. Figure 2-11 and show the calibration curves, blood glucose level calculation, and EGA results for each subject in 1-s-normalization process.

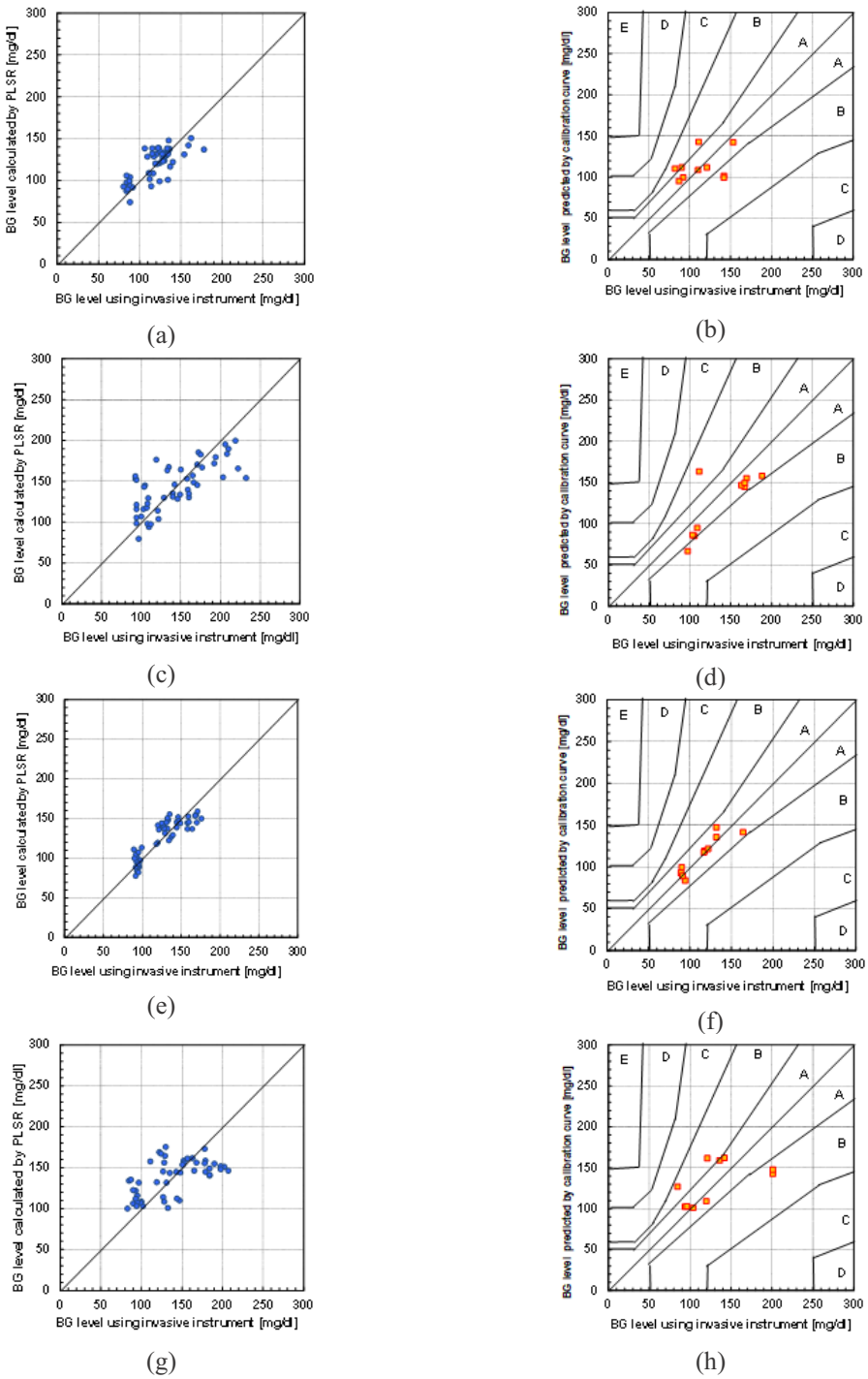


Figure 2-9 Left: Calibration curves for (a) Subject A, (c) Subject B, (e) Subject C, and (g) Subject D. Blood glucose concentrations in these plots were estimated PLSR with shortest-time-cut process. Right: Validation results for (b) Subject A, (d) Subject B, (f) Subject C, and (h) Subject D. Blood glucose concentrations in these plots were estimated using the corresponding calibration curves.

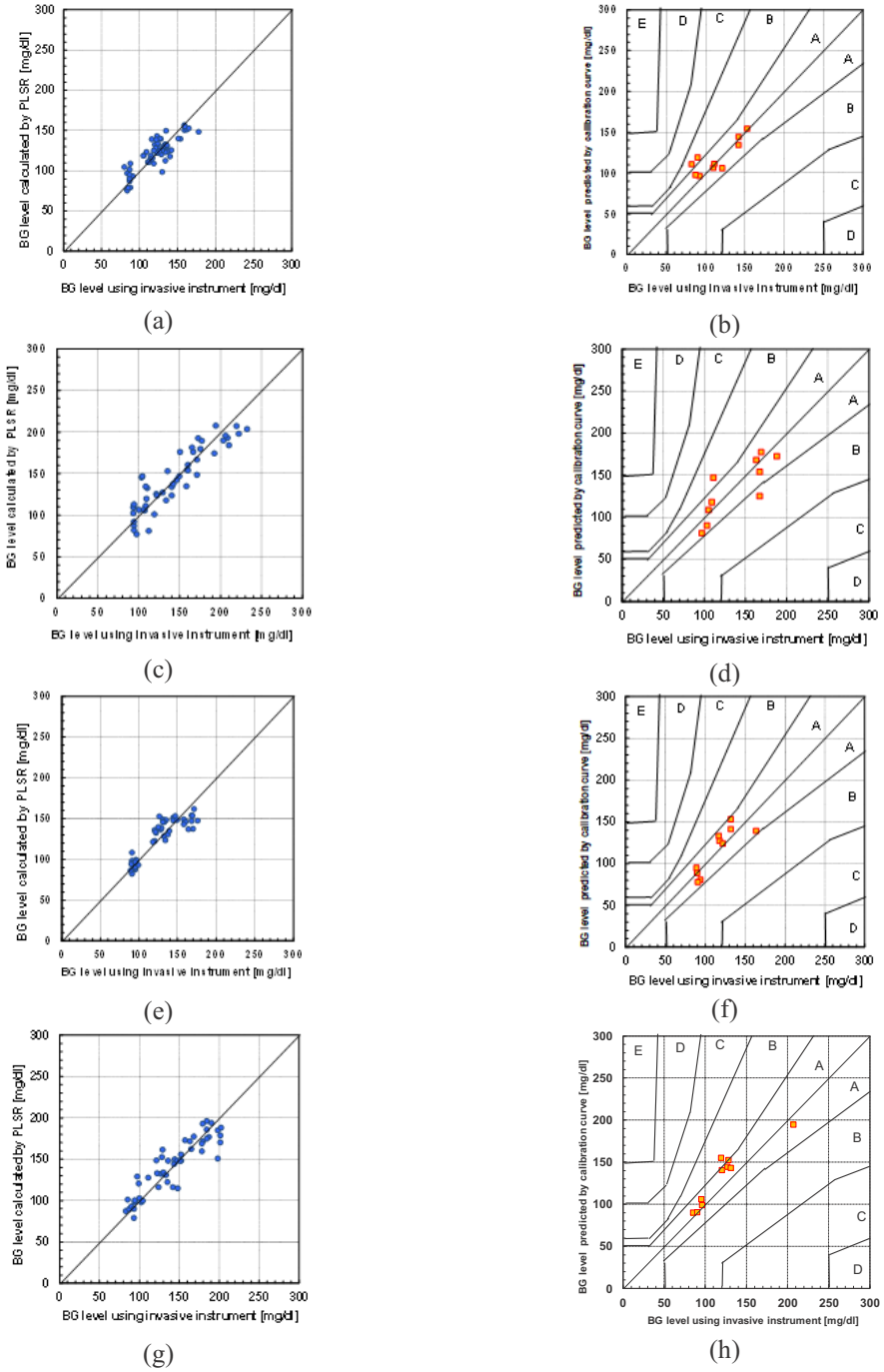


Figure 2-10 Left: Calibration curves for (a) Subject A, (c) Subject B, (e) Subject C, and (g) Subject D. Blood glucose concentrations in these plots were estimated using PLSR with 1-s-normalization process. Right: Validation results for (b) Subject A, (d) Subject B, (f) Subject C, and (h) Subject D. Blood glucose concentrations in these plots were estimated using the corresponding calibration curves.

Table 2-3 Calibration curve and validation results for each subject.

Subject		A		B		C		D	
Processing Method		Shortest	1-s	Shortest	1-s	Shortest	1-s	Shortest	1-s
Calibration result	SEC (mg/dL)	17	15	34	21	15	14	33	19
	r	0.67	0.77	0.58	0.86	0.84	0.87	0.44	0.86
	factors	4	4	4	4	4	4	4	4
Validation result	SEP (mg/dL)	20	10	23	16	7	12	26	14
	A-zone (%)	60	80	80	80	100	100	50	90
	B-zone (%)	40	20	20	20	0	10	50	10

Referring the Figure 2-9 and Figure 2-10, the EGA results of all the subjects are plotted in the clinically effective zones A and B. However, SEP in the shortest-time-cut process was 26 mg/dL in subject D like showed in Table 2-3. Since the average blood glucose level in the validation data set of subject D is 129 mg/dL, SEP is approximately 20%. This result is remarkably poor. On the other hand, in result of the 1-s-normalization process, the correlation coefficient of the calibration curve of three subjects exceeded 0.8, and in the EGA result, 80% of the data or more were plotted in zone A. Furthermore, SEP is 10–16 mg/dL, which is of the same level as the measurement error of commercially available invasive blood glucose measurement systems. The SEP of the 1-s normalization process method was better than that of the shortest-time-cut

processing, as indicated in Table 2-3. This SEP result is 9–12% of the average blood glucose value in the validation data set. These results are very good for calculating blood glucose level.

The reason why the precision of blood glucose level calculation greatly differs by two signal processes is verified. In Figure 2-11b, the blood glucose levels calculated from the reference blood glucose levels 85, 121 mg/dL (“low” in the Figure 2-11b) and 187, 202 mg/dL (“high” in the Figure 2-11b) pulse wave signals were 127, 165 and 145, 143 mg/dL, respectively. These calculated blood glucose levels vary differ from the reference blood glucose level. In order to verify this cause, the calculated calibration curve is confirmed. In Figure 2-11a, the data on the reference blood glucose level of approximately 85 and 125 mg/dL are overestimated, and the data in approximately 180 and 200 mg/dL are underestimated. Therefore, the calibration curve that is constructed by this signal processing adversely affects the calculation of the blood glucose level. This phenomenon also appeared for subject B. On the other hand, in Figure 2-11d of the validation result in the 1-s-normalization process, the same four reference blood glucose values are plotted around Y = X, and the blood glucose level is calculated with high

accuracy. Accordingly, SEP values were also better with the 1-s-normalization process. The SEC value of the 1-s-normalization process for subject D is much better than those of the shortest-time-cut process. The calibration curve shown in Figure 2-11c is also plotted around the axis of Y = X. Therefore, in the 1-s-normalization process, reference blood glucose levels were correctly calculated. The data constituting these calibration curves are the same, and only the processing method of normalization of the horizontal axis (measurement time) of the 1-pulse pulse wave is different.

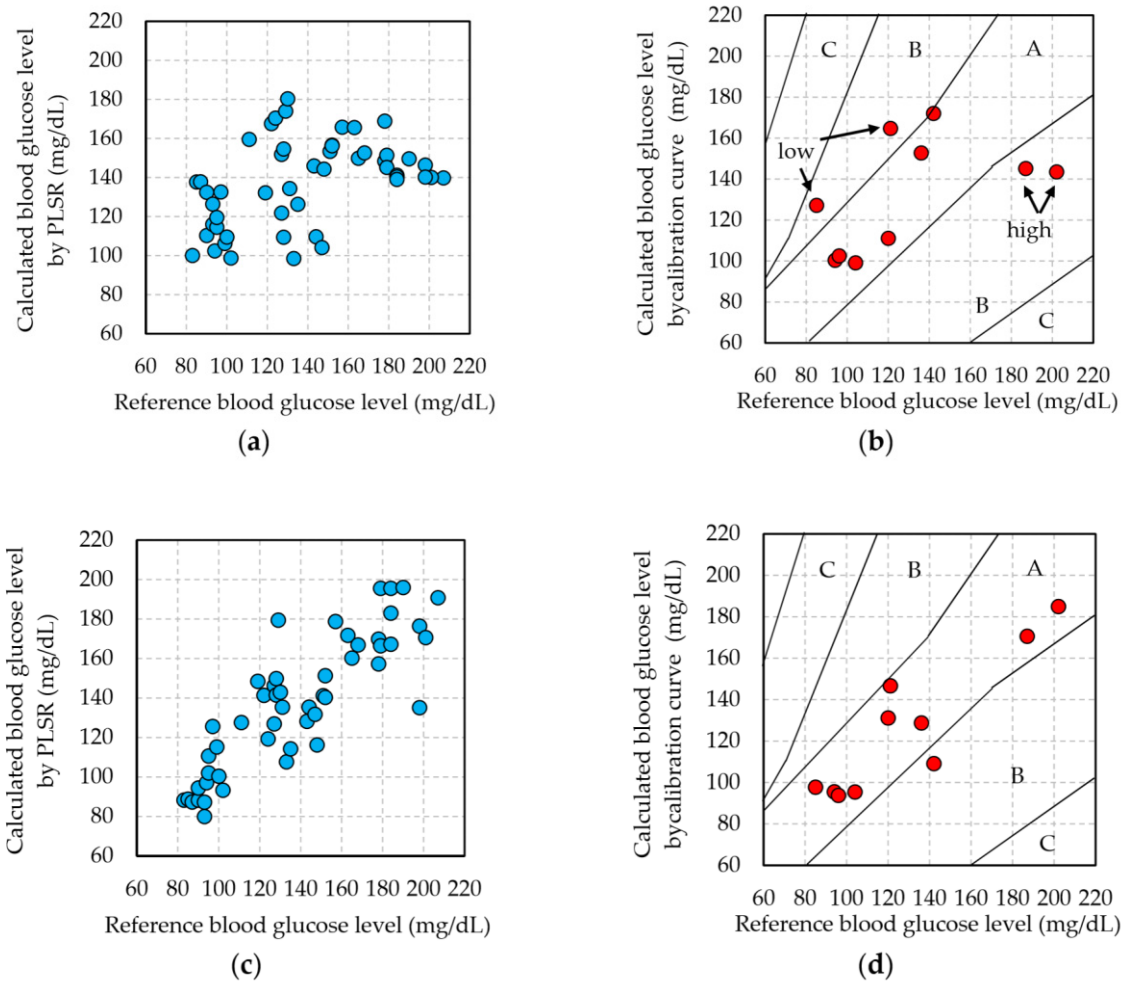


Figure 2-11 Calibration curve and validation results for calculated blood glucose level (Subject: D, shortest-time-cut and 1-s-normalization processing).

(a) Sub.D-calibration curve in Shortest;

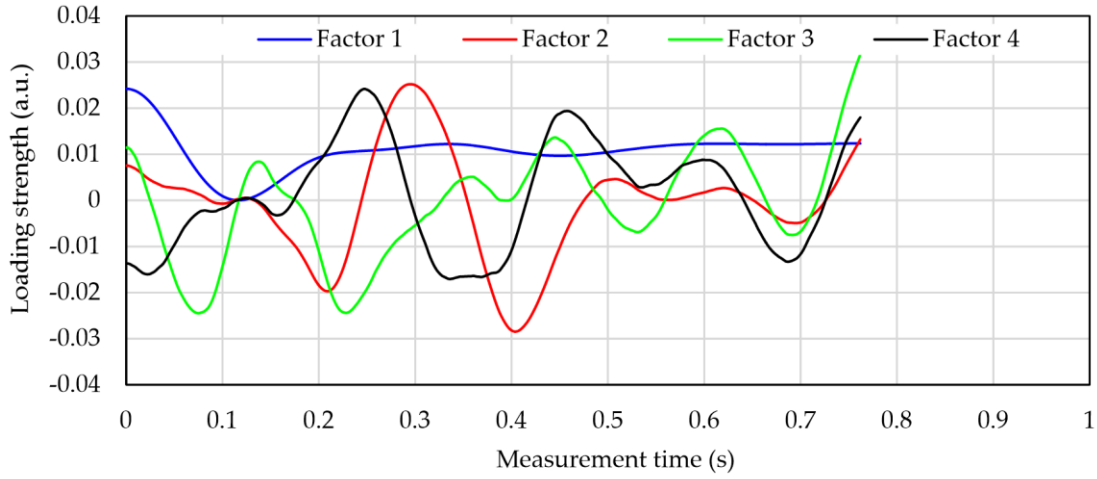
(b) Sub.D-validation result in Shortest;

(c) Sub.D-calibration curve in 1-s;

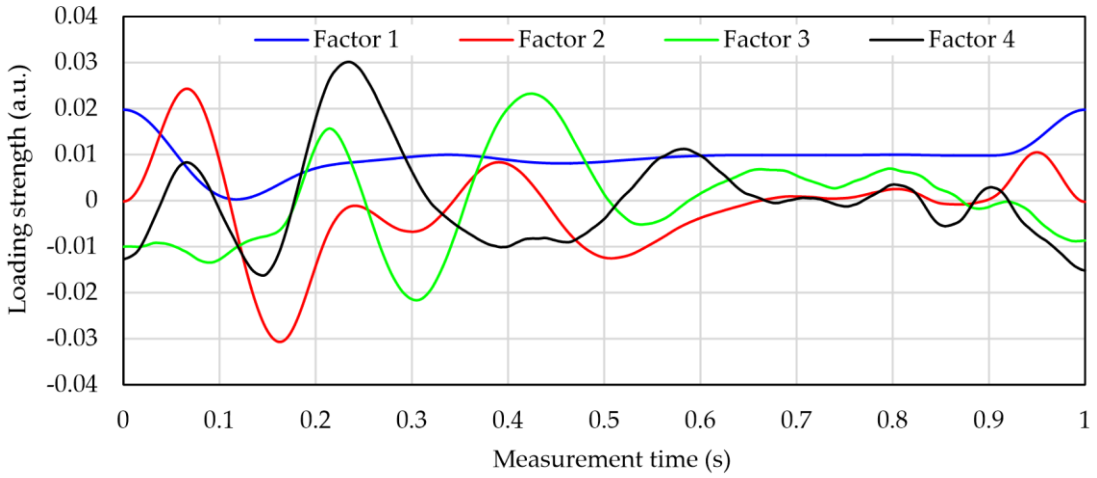
(d) Sub.D-validation result in 1-s.

2.3.3 Adequacy of Non-Invasive Blood Glucose Measurement

In former Section, it was shown that the calculation of blood glucose level is better with the 1-s-normalization process than with the shortest-time-cut process. The influence on curve was verified. A normalized pulse wave signal for a blood glucose level close to the highest, lowest, and average values for subject D processed by each normalization method was shown in Figure 2-8. The normalized wavelength shift of the pulse wave signal in the shortest-time-cut process is 0 at approximately 0.12 s for all of the blood glucose levels, and the pulse wave signal after approximately 0.75 s has been deleted. On the other hand, in the 1-s-normalization process, the measurement time of the pulse wave signal at which the wavelength shift is 0 varies among different blood glucose levels.



(a)



(b)

Figure 2-12 Loading vector of calibration curve in subject D. (a) Loading vector of calibration curve in shortest-time-cut process; (b) Loading vector of calibration curve in the 1-s-normalization process

Figure 2-12 shows the loading vector of each factor that is used for constructing the calibration curve in each processing method for subject D. The loading vector indicates the dependence of each factor on the calibration curve. The greater the absolute value on the vertical axis is, the more significantly the wavelength shift at that time depends on the blood glucose level calculation. In Figure 2-12, the loading vector at Factor 1 in each processing method is similar to the pulse wave signal. In the loading vector of factor 2 (Figure 2-12b red line) of the calibration curve in "1-s-normalization process" with high calculation accuracy, the absolute values are 0.07 s and 0.16 s on the positive and negative side, respectively. The numerical value on the vertical axis at Factor 1 is 0 at 0.12 s. Therefore, the loading vector of factor 2 affects the change in inclination around peak B in Figure 2-8b. These inclinations are affected by the time-axis direction (horizontal-axis direction), since peak A in Figure 2-7b is normalized to "1" and peak B is normalized to "0." Furthermore, in the loading of the 1s-normalization process in Figure 2-12b, Factor 1 has a large peak after 0.92 s, and Factor 2 has a large peak at 0.95 s. These are the rising parts of peak A in Figure 2-7b. Therefore, normalized calibration curves that capture the features of inclinations around peaks A and B is calculated

the calculation of blood glucose level in high accuracy.

On the other hand, in the loading vector of factor 2 (Figure 2-12a red line) of the calibration curve in “shortest-time-cut process” with low calculation accuracy, the absolute value is 0.3 s on the positive side and 0.4 s on the negative side. It shows almost 0 at 0.07 and 0.16 s. At these measurement times, the absolute value of loading of factor 3 (Figure 2-12a green line) is large, however this value is smaller than the absolute value of factor 2 in “1-s-normalization process”. Therefore, the change in inclination around the peak B in Figure 2-7b is not shown in each factor of the calibration curve in “shortest-time-cut process”. In addition, the absolute values of factors 2, 3, and 4 after 0.7 s are large, and this information has a big influence. However, in Figure 2-8a, since there are no characteristic peaks after 0.7 s, information unrelated to the pulse wave signal is indicated in the factor. Since the rising part of peak A in Figure 2-7b after 0.92 s has been deleted by “shortest-time-cut process”, the influence of the pulse wave signal in this part is not included in each factor.

From the above, the calculation of the blood glucose level from the pulse wave signal is greatly affected by signal processing on the “Measurement time” axis, which is a feature of the “1-s-normalization

process". In the 1-s-normalization process, this influence of the time-axis direction is well captured. The calculation of the blood glucose level is significantly influenced by the inclination of the pulse wave signal around the peak A and B in Figure 2-7 b. In other words, the blood glucose level is not exactly the magnitude of the pulse; rather, it is significantly dependent on the blood flow in the time-axis direction.

The causes of changes in the blood flow due to the blood glucose level may be as follows.

- More glucose was contained in blood after a change in the blood glucose level; consequently, the blood flow changed because of a change in blood viscosity.
- Since glucose is sent into the body, the blood vessels expanded at the time of hyperglycemia, and the blood flow changed.

Medical verification to confirm these causes is a future task.

2.4 Conclusions

This Chapter 2 reported a revolutionary method of non-invasive blood glucose measurement using an FBG sensor system. Pulse wave signals

were measured for four subjects, and blood glucose levels were calculated using two signal processing methods. Consequently, we found that the blood glucose level that was calculated with the shortest-time-cut process had poor measurement accuracy above 200 mg/dL. The blood glucose level calculated with the 1-s-normalization process had good measurement accuracy overall. Moreover, the acquisition of the slopes of peaks A and B of the pulse wave signal from the loading vector of the calibration curve in each signal processing method improved the accuracy of calculation of the blood glucose level. Lastly, we found that calculating the blood glucose level from the pulse wave signal with high accuracy, the blood flow should be considered.

Our results indicate that the blood glucose level can be reliably calculated from the pulse wave signal measured by the FBG sensor. However, it is necessary to medically verify the relationship between the blood glucose level and blood flow. When this relationship becomes clear, the calculation of blood glucose level from the pulse wave signal would be theoretically validated.

To perform this verification, it is necessary to investigate the blood flow while the blood glucose level is changing. However, it is not possible to measure the blood flow by performing incisions on the subject. Therefore, we plan to use ultrasonic tomographic imaging equipment [31], which can

image the inside of the body from the outside, to measure the blood flow. In this experiment, this device will be placed at the same location as the FBG sensor: the radial artery of the subject. The subject ' s blood glucose level will be intentionally changed, and simultaneous measurements will be performed using the FBG sensor and the ultrasonic tomographic imaging device. Then, the blood flow and the diameter of the blood vessel will be measured using the ultrasonic tomographic imaging device. The relationship between the measurements of the ultrasonic tomographic imaging device and the shape of the pulse wave signal detected by the FBG sensor will be investigated for each blood glucose level.

We have already reported that the pulse rate, respiration rate, and blood pressure can be calculated simultaneously and continuously from the pulse wave signal that is measured using an FBG sensor system [21], [32]. If non-invasive blood glucose measurement is also included the abovementioned list, an FBG sensor system can be used as a convenient multi-vital-sign sensor. For diabetic patients, we aim for real-world implementation as soon as possible.

Chapter 3
Feature extraction of blood glucose using neural network

Chapter 3
Feature extraction of blood glucose using neural network

3.1 Introduction

We figured out the correspondence between the pulse wave which got from FBG sensor system and reference blood glucose level using basic analysis method Partial Least Squares Regression (PLSR), from previous chapter [33]. Previous chapter reported that the correspondence is significantly effective as a measurement method, however, there are some unclear points. Later, the relation between the pulse wave form and arteriosclerosis have been reported [34], subsequent, the relation between the pulse wave form and diabetes was also reported [35]. Those reports aim for the diagnose the arteriosclerosis or diabetes, not for measuring the concrete values. Taking in the current tendency for elucidation of mechanism, this report states that the effectiveness of the measuring method using machine learning for getting more robustness as a measurement method, reinforcing

the correspondence which we reported in previous chapter between the pulse wave form and blood glucose level. In recent years, machine learning has been used in various applications. It is also applied for medical purposes, such as diagnosis of retinopathy from retinal images [36] and diagnosis assistance for Alzheimer's disease [37]. For other instance, Artificial Neural Network was applied for construct calibration curve in blood glucose measurement [16].

Moreover, this fiber shape promotes the revolutionary way to utilize, like weaving into textile, taking advantage of the robustness against water and wash and un-necessity of disposable items. Adapting FBG sensor as a vital sign monitoring device is not only for creating one of glucose sensor, but also establishing smart textile or various products [11].

This Chapter 3 describes that the new non-invasive blood glucose measurement method which makes use of machine learning techniques and an FBG sensor. Our technique employs the FBG sensor to obtain pulse wave pattern data characterizing arterial blood flow, which can be affected by glucose concentration. Subsequently, we employ machine learning to relate complex pulse wave pattern data to blood glucose levels.

3.2 Material and methods

This chapter states about the trial that applying new analysis method to the same data sets with Chapter 2. Figure 3-1 Schematic flow of the calibration and validation process. show the schematic flow of the entire experiment.

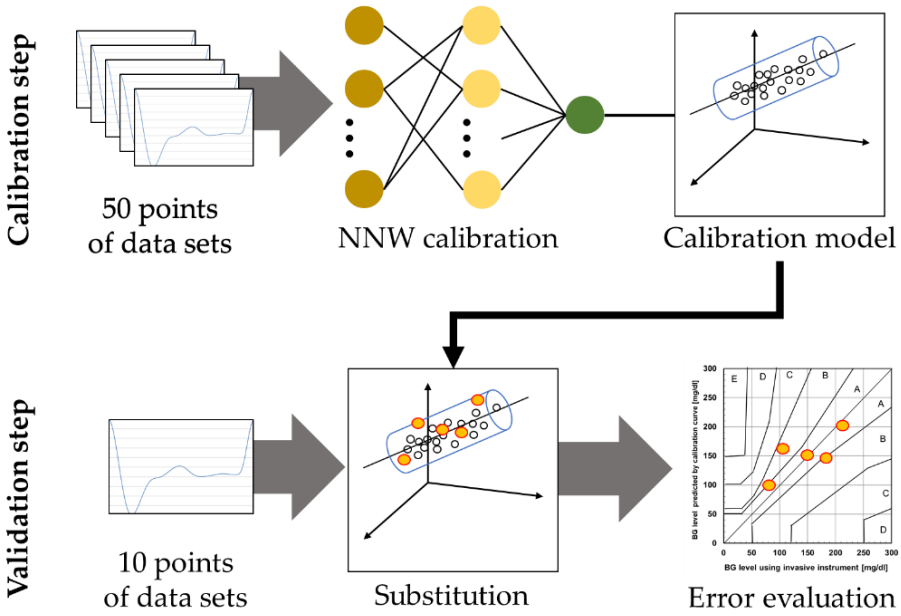


Figure 3-1 Schematic flow of the calibration and validation process.

3.2.1 Measuring instruments

The non-invasive measurement system developed in this study requires the construction of a calibration curve. For this, in addition to signals from the FBG sensor, reference values need to be obtained from current blood glucose measurement instruments. Those are AntsenseIII

(HORIBA Co., Ltd., Kyoto, Japan) or FreeStyle Precision Exceed H (Abbott Japan Co., Ltd., Osaka, Japan). This blood glucose level is used as the reference blood glucose when the pulse wave signal is measured.

Pulse waves were measured using the PF25-S01 FBG sensor system (Nagano Keiki Inc., Japan), [38] configured according to the specification summarized in Table 2-1.

3.2.2 Pulse Wave Measurement

In this experiment, 60 measurements were obtained for each subject. Four healthy males in their twenties were selected for participation. While measurement for each subject was completed at an arbitrary time of day over several hours, we began each measurement from a subject's hungry state, prior to them having a meal. To measure a subject's pulse wave, the FBG sensor was attached to their skin, at a point corresponding to the radial artery, using adhesive medical tape. The subjects lay in a supine position, and their wrists were kept level with their heart. Figure 2-3 depicts a pulse wave measurement, illustrating the typical posture of a subject during this process. Measurement was completed in ~20 seconds, which is the cycle time

required for an automatic sphygmomanometer to obtain a stable measurement. Smoothing was then applied to each signal, at a 1 kHz sampling frequency. Then, each pulse wave was filtered using a bandpass filter with a pass band of 0.5–5 Hz. Next, the amplitudes of the signals were normalized, with the maximum set at 1 and the minimum at 0. Each peak in the signal was selected before it was subsequently normalized signal with respect to time, such that there were 1000 data points on the horizontal axis of each plot. Finally, each signal was averaged to yield a pulse wave. This procedure is described in Figure 2-6.

3.2.3 Blood Glucose Measurement

Blood glucose measurements were performed at the same time as pulse wave measurements using invasive-type instruments, to obtain reference blood glucose values. We chose invasive-type instruments which be available in market for person has diabetes. Therefore, pricking needle and blood sampling were required for experiment protocol. The protocol for this study was approved by the Ethics Committee of Shinshu University (Project identification code: No. 3202,

Verification clinical trial with wearable vital sign measurement system).

3.2.4 Machine Learning: Hierarchical type NNW

For our machine learning model, the 60 pairs of pulse wave and blood glucose level data were first arranged, with pulse wave data defined as the explanatory variable, and blood glucose levels defined as the reference. Subsequently, 50 pairs of data were randomly selected, for constructing the calibration curve. The remaining 10 pairs of data were used to validate the calibration curve.

We created our machine learning model using a hierarchical NNW from the MATLAB toolbox, adopting an error propagation method as the learning technique. In addition to the steepest descent method, which is a basic weight update method, we included a weight update method with a moment term, and one that adaptively modifies the learning rate, as fast convergence algorithms. The model featured a three-layer structure consisting of an input layer, an intermediate layer, and an output layer. Learning parameters for the model, adopted from previous chapter, are summarized as follows. The learning rate was set

to 0.1, the learning rate reduction coefficient was set to 0.9, the learning rate increase coefficient was 1.03, and the momentum coefficient was 0.85. The number of middle layer units was 1000 and the number of output layer units was 1. The learning termination condition occurred either when the learning limit was reached, or a mean squared error of 10-4 was achieved.

3.2.5 Error Grid Analysis (EGA)

Same with former chapter, Error grid analysis (EGA) was used for validating the blood glucose levels estimated using our measurement method. EGA determines that a method is clinically acceptable if all results are in zones A and B like written in Figure 2-11. In this study, the goal is that the all validation results are in the A or B zone.

3.3 Results

3.3.1 Blood glucose levels

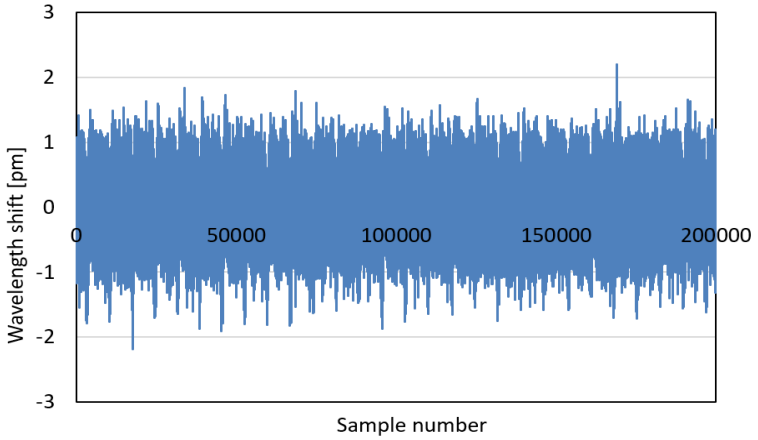
As blood glucose levels for each subject change in response to their activity, such as having a meal or resting, to be suitable for blood

glucose calibration, reference values should also vary in a wide range as subject possible. We obtained reference blood glucose levels using currently available measurement instruments, for each subject as follows. Subject A: 178–81 mg/dl, Subject B: 232–93 mg/dl, Subject C: 168–88 mg/dl, Subject D: 207–83 mg/dl.

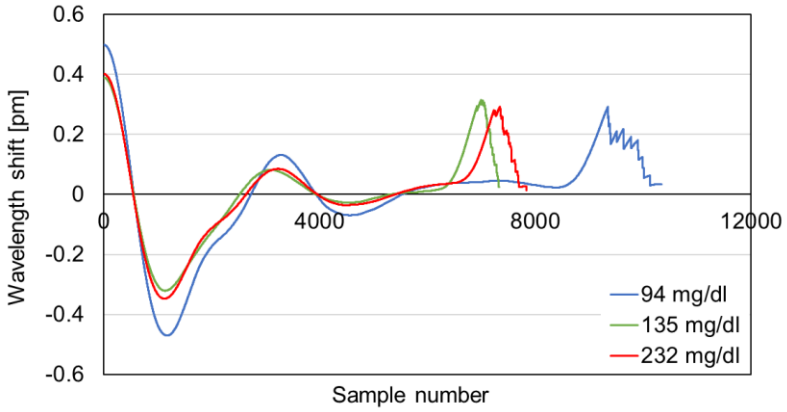
3.3.2 Pulse waves

Figure 3-2 (a) shows the raw signal from FBG sensor system, blood glucose level is 135 mg/dl. Next, Figure 3-2 (b) shows typical pulse waves obtained from Subject B, corresponding to the maximum, minimum, and average blood glucose levels recorded. These signals represent the filtered and average over a single time period. Filter is band pass type, frequency 0.5 ~ 5.0 Hz were only passed. Due to the differing lengths of the time-axis, noise is encountered at the end of each signal. This difference in length is caused by a physiological phenomenon called respiratory sinus arrhythmia, which cannot be removed. These three graphs show that each pulse wave looks similar, regardless of the blood glucose level. As it is difficult to distinguish them just by sight, mathematical analysis methods are required. In order

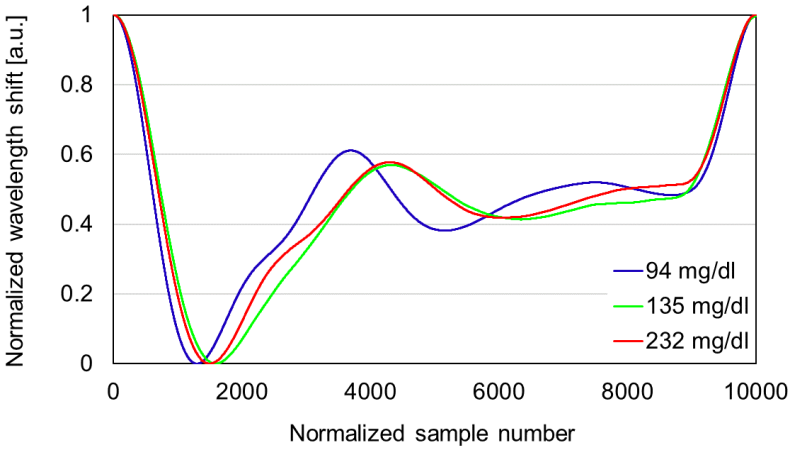
to be applied for those analysis methods, noisy part was cut, signals were applied normalization with horizontal axis and vertical axis like showed in Figure 3-2 (c).



(a) Raw signal with 135 mg/dl



(b) Averaged pulse in one measurement



(c) Normalized pulse wave

Figure 3-2 Pulse waves recorded from Subject B with their blood glucose levels at their minimum, mean, and maximum values.

3.3.3 Calibration and validation

Calibration curves were constructed for the four different subjects using the pulse waves described in the preceding section. Figure 3-3 shows calibration and validation results for blood glucose measurement. Plots on the left are calibration models for each subject, based on NNW analysis, while plots on the right are EGA of 10 datasets obtained from these subjects, for validation of the calibration curves. Table 3-1 lists results of calibration and validation. The correlation coefficients for all the subjects were over 0.9. Similarly, the SEC values were small, indicating that calibration was completed to a high degree of accuracy. While some deviation could be observed between each subject's SEP, EGA demonstrated that results occupied only the A and B zones of these plots, indicating that the error in the system is small enough to be ignored in practical medical situations. These validation results are clinically acceptable [26], suggesting that the proposed method is able to measure blood glucose levels adequately.

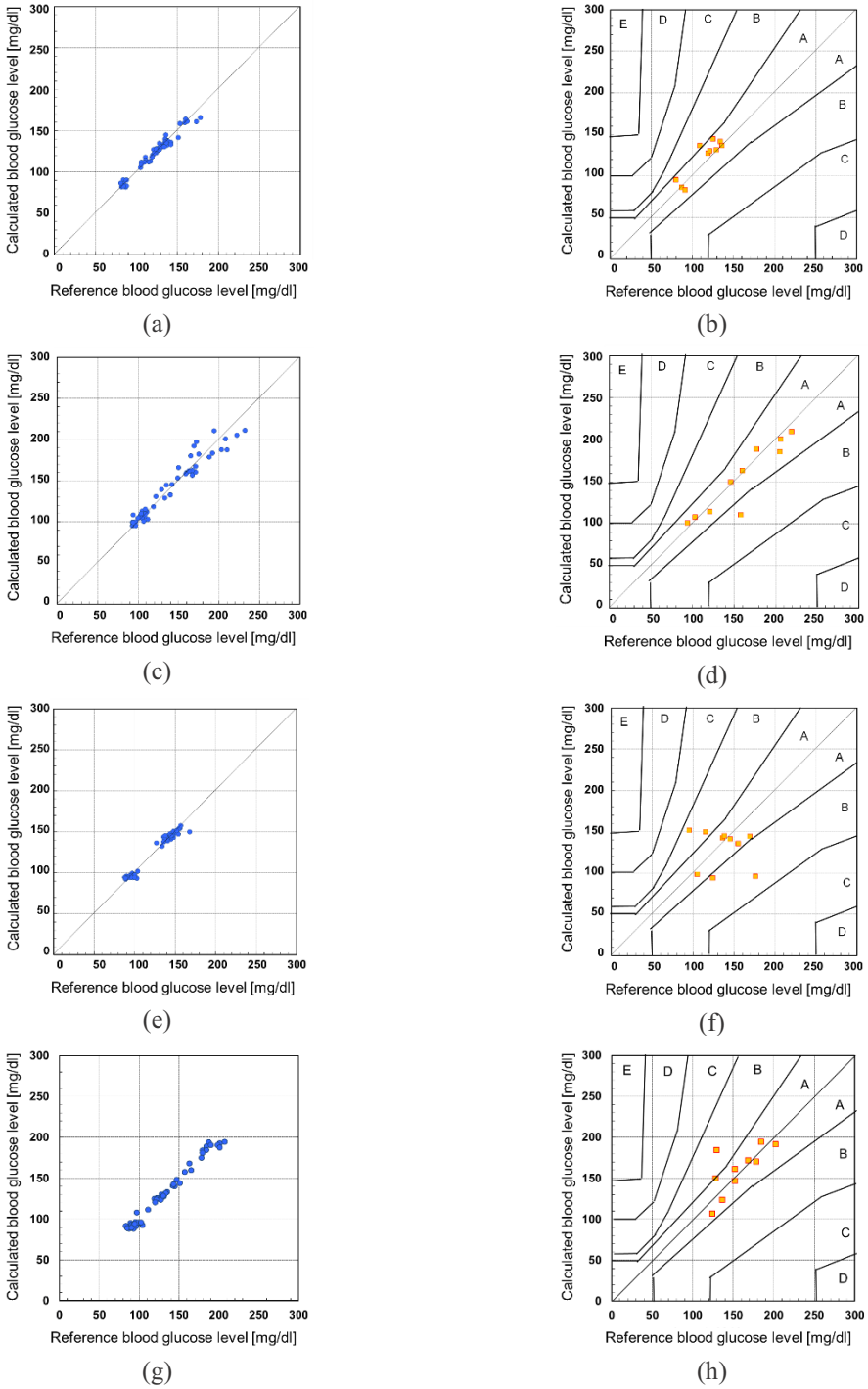


Figure 3-3 Left: Calibration curves for (a) Subject A, (c) Subject B, (e) Subject C, and (g) Subject D. Blood glucose concentrations in these plots were estimated using a neural network. Right: Validation results for (b) Subject A, (d) Subject B, (f) Subject C, and (h) Subject D. Blood glucose concentrations in these plots were estimated using the corresponding calibration curves.

Table 3-1 Results of the calibration and validation

	Subject	A	B	C	D
PLS calibration	r	0.98	0.97	0.98	0.99
	SEC [mg/dl]	5	10	5	5
Validation	SEP [mg/dl]	14	18	38	22
	A-zone [%]	90	90	60	90
	B-zone [%]	10	10	40	10

SEC: standard error of calibration, SEP: standard error of prediction,
r: correlation coefficient

3.4 Discussion

3.4.1 NNW Calibration models and validation

We obtained high correlation coefficients from all subjects' calibration curves, and a maximum SEC of 10, which is often considered to be small with regard to blood glucose instruments. This finding indicates that not only do signals from radial arteries obtained by FBG sensing contain information about the blood glucose level, NNW models are able to extract meaningful information from these signals. This experiment which is equivalent to the first trial for apply NNW is not sophisticated toward the machine learning yet. The analysis condition stated here may just be a one of the ways to analyzes which may be presence a lot. This trial could not adopt to use the high specification computer which be loaded GPU for calculating. When it is available to use, we should validate the expand the limitation which we have. Especially, this time, the number of middle units were limited to 1000, due to the consuming time. The more suitable condition should be appeared with high frequency processor.

We also note that all the validation points are plotted in the A or B zones, suggesting that the system we are proposing is capable of

highly accurate measurement. However, there were differences between each subject's SEP score, which ranged between 14 and 38 mg/dl. In particular, the SEP scores for Subjects C and D were remarkably high. Focusing on Subject C, who had the biggest SEP, only 60% of data was in the A zone of the EGA plot, the lowest in this study. For analysis of this phenomenon, the ranges of blood glucose levels obtained in validation are listed below, for comparison with the reference values listed in the results section.

Subject A: 136 mg/dl – 80 mg/dl.

Subject B: 214 mg/dl – 94 mg/dl.

Subject C: 176 mg/dl – 95 mg/dl.

Subject D: 202 mg/dl – 124 mg/dl.

Referring list, each subject has blood glucose range, 56 mg/dl, 124 mg/dl, 81 mg/dl, and 78 mg/dl. We can find subject C and D has narrow blood glucose range, compare with subject A and B. Especially, we note that for Subject C, the range of the blood glucose values is about 80 mg/dl in both calibration and validation. In addition, we also note from Figure 3-3 (e) that data points for Subject C are grouped into two distinct clusters. Further investigation revealed that Subject C's blood glucose level changed drastically because of the glucose load of their

regular lunch, causing the unnatural plots observed. Hence, the calibration curve for Subject C was optimized for narrow and divided range of blood glucose level data sets, causing the bigger SEP. However, regardless of their larger SEP scores, a high correlation coefficient was still obtained in calibration with data from Subjects C and D. High correlation coefficient will not always directly show the good calibration in this case, we need to pay attention to validation data more. To improve this error, data gathering should be repeated with a wider and continuous range of blood glucose levels. However, about this time's result, we didn't show the any plot in zone C, D and E, means there is only small error which we can ignore clinically. Moreover, correlation coefficient was quite high. There is no room for doubt there are some relationship between blood glucose level and pulse wave.

On the other hand, validation methods do not provide the validation with over individual person, this time. Pulse wave form depend on each person, unprepared individual calibration and validation lead bigger error, for now. This matter is problem for validity and certainty of measurement, we are going to work and discuss against those problems in future. Moreover, the characteristic blood glucose range of healthy subjects and subjects with diabetes differ. Healthy

person is difficult to show the over 200 mg / dl blood glucose level, on the other hand, person with diabetes often show the over 300 or 400 mg / dl blood glucose level. Therefore, this paper's result is limited as just for healthy blood glucose level, we need validation with quite high blood glucose level, we need more detailed validation is required. There are a lot of steps which we have to make it clear before practical use, this paper leads various follow up studies.

3.4.2 Blood glucose measurement using FBG sensors

We conducted our experiments based on the assumption that continuous pulse wave signals obtained from FBG sensor systems contain information about blood glucose levels, since these signals are similar to the acceleration pulse wave (the second derivative of the fingertip volume pulse wave signal) [18]. Thus, the presence of a correlation between blood glucose level and FBG signals is to be expected, based on the results of the former study. However, in spite of this correlation, there was no visible concrete correspondence or relationship between these two parameters, as shown in Figure 3-2 at a

glance. Referring to the former study, multivariate analysis can make such a correspondence clear [12, 20]. We enumerate some physiological factors suggesting the validity of using pulse wave pattern data for blood glucose sensing below, which also serve as explanations for why the correspondence between the two parameters is not immediately clear.

The primary reason for measuring blood glucose with FBG sensors is that blood viscosity is generally considered to change according to glucose concentration. In the former study, it was noted that prediction accuracy improved when the latter part of a one pulse wave signal was considered with two way of analysis, indicating that the change in blood glucose level caused a change in blood flow with respect to time [12]. Thus, it can be said that blood viscosity or elasticity alters blood flow, leading to a change in the nature of the pulse wave. However, viscosity can change clearly with quite high concentration of glucose solution, on the other hand, low concentration of glucose solution which human might show could not see the clear correspondence between with viscosity and concentration of glucose. This phenomenon is verified our preliminary study. Now, we think the effect of the viscosity is not dominative, just a one of small factor for

detecting blood glucose.

In addition, we consider FBG sensor operation, particularly, the effect of anatomical structures on sensor response. Concretely, as FBG sensors are strain sensors, the thickness of structures such as blood vessels, skin, and tissue can affect their response. Different studies have noted the relationship between blood glucose and blood vessel stiffness, with elevated blood glucose promoting arteriosclerosis over a long time period. Similarly, over short time periods, high blood glucose level states are also able to change the osmotic pressure of blood plasma. Other reports have stated that both short- and long-term exposure to “High Glucose” and “High mannitol” states decreased the expression of the active, phosphorylated form of endothelial nitric oxide synthase (Ser1146-eNOS), and, in parallel, increased the expression of the vascular cell adhesion molecule (VCAM)-1 protein. The presence of glucose also affects cell generation and metabolism, as has been detailed elsewhere previously. This report concludes that correction of hyperosmolarity by targeting its osmosignaling pathway may thus represent a novel strategy to counteract the detrimental vascular consequences of diabetic hyperglycemia [39]. We have been considering these phenomena could be one of valid principle for sensing

blood glucose.

Finally, research conducted by Li et al. [34] has demonstrated significant differences between the shapes of pulse waves obtained from healthy subjects and subjects with diabetes, in both the amplitude of the wave, and with respect to time. This study quantitatively assessed changes in arterial pulse waveform parameters in patients with type 2 diabetes. These changes are in addition to the delay of blood flow that has been used as an indicator for arteriosclerosis. Consequently, they were able to conclude that the pulse waveform characteristics could be used as indices of arterial stiffness in patients with type 2 diabetes [34]. Moreover, there are also interesting research about pulse wave and diabetes. This reports study about relationship between pulse wave shape and diabetes. They conclude that the results demonstrated that the noninvasive and convenient pulse-taking diagnosis described in this paper has the potential to become a low-cost and accurate method to monitor the development of diabetes [35].

These studies all indicate a variety of ways in which blood glucose level can affect strain, highlighting the validity of using FBG sensors for measurement. However, as the combination of these effects is complex, a suitable classification method is required to obtain

accurate blood glucose data, explaining our use of machine learning techniques.

3.5 Conclusion and prospects

Our technique consists of data gathering using the FBG sensor system, construction of a calibration curve using NNW analysis, and subsequent estimation of the blood glucose level. Data calibration and validation was conducted with four subjects, and errors were evaluated using EGA, designed specifically for blood glucose instruments. All validation data points were plotted in the “safe zone,” indicating that FBG sensor system and analyzing method are suitable for non-invasive blood glucose measurement. That's why, we can conclude that the blood glucose level can be calculated from the pulse wave with NNW.

However, we note a limitation in this study, in that all subjects were healthy young males. From previous chapter it has been noted that the characteristic blood glucose range of healthy subjects and subjects with diabetes differ. To ensure that this technique is valid with diabetic patient, experiments should be conducted with the cooperation of subjects with

diabetes, and with a wider demographic, as supervised by an accredited institution. In addition, the effects of prolonged high-blood glucose levels should be simulated. This report is just a first step of the development.

Nevertheless, the success of our technique suggests that the creation of a wearable measurement device is viable. The FBG sensor's fibrous shape makes it suitable for inclusion in a smart textile or garment, particularly as we have already developed some surface treatment techniques that enable the weaving of these devices. Incorporation of these devices into smart textiles would lead to the creation of a revolutionary product: a "wearable multiple vital sign measurement device." The combination of the demand for continuous blood glucose monitoring, these surface treatment techniques, and our promising FBG sensor findings suggest that the establishment of such wearable devices is not far in the future.

Chapter 4
Trial for acquisition of vital signs in bed-environment

Chapter 4
Trial for acquisition of vital signs in bed-environment

4.1 Introduction

Quality of sleep is important for performance and wellbeing of people. The thermal environment people are exposed to be important for the sleep quality. Therefore, control of the thermal environment during sleep is important. One control possibility is to measure and use body physiological signals in response to the thermal environment. During the recent year's continuous measurement of blood pressure changes during sleep has attracted much attention because of "Early morning hypertension" or "Nocturnal hypertension" studies. However, good devices which can monitor sleeping person with waking up had never been appeared. We need vital sign monitoring device which can measure blood pressure without preventing comfortable sleep.

In order to achieve, this task, we consider FBG sensor system can be one of a good solution. Former study already reports the application of FBG

sensor for pulse rate, breathing rate, stress loading, blood pressure and blood glucose measurement [22], [33]. Especially, bed-environment is surrounded by a lot of textile products. FBG sensor system can achieve vital sign monitoring just by one optical fiber. By weaving FBG sensor to the various textile products, ideal measurement condition can be proposed without preventing comfortable sleep.

Hence, there are some merit for introduce FBG sensor system to bed environment. However, measuring situation is different with former experiments. Hence, this Chapter reports the first trial that what kind of signal can we get from the sleeping person for introducing FBG sensor system to the bed-environment.

4.2 Material and methods

4.2.1 FBG sensor system

In this experiment, FBG sensor and an interrogator unit (SMART FIBERS co. LTD: Smart Scan SBI Single Board Interrogator) compose the system. This interrogator is relatively small compare with former chapter's interrogator, and possible to detect strain with 10 channels. Instead of multi-channel detection, this device has some

limitation with sampling rate, does not have the stiff machine box, like showed in Figure 4-1. Specification detail are described below in Table 4-1

Table 4-1 Specification of Smart Scan SBI

Measurement and processing	Smart Scan SBI
Central Bragg wavelength [nm]	1550
Tolerance of Bragg wavelength [nm]	±0.5
Type	Single mode fiber colorless
Material	SiO_2
Recoating material	UV resin
Diameter [µm]	250
Core diameter [µm]	10

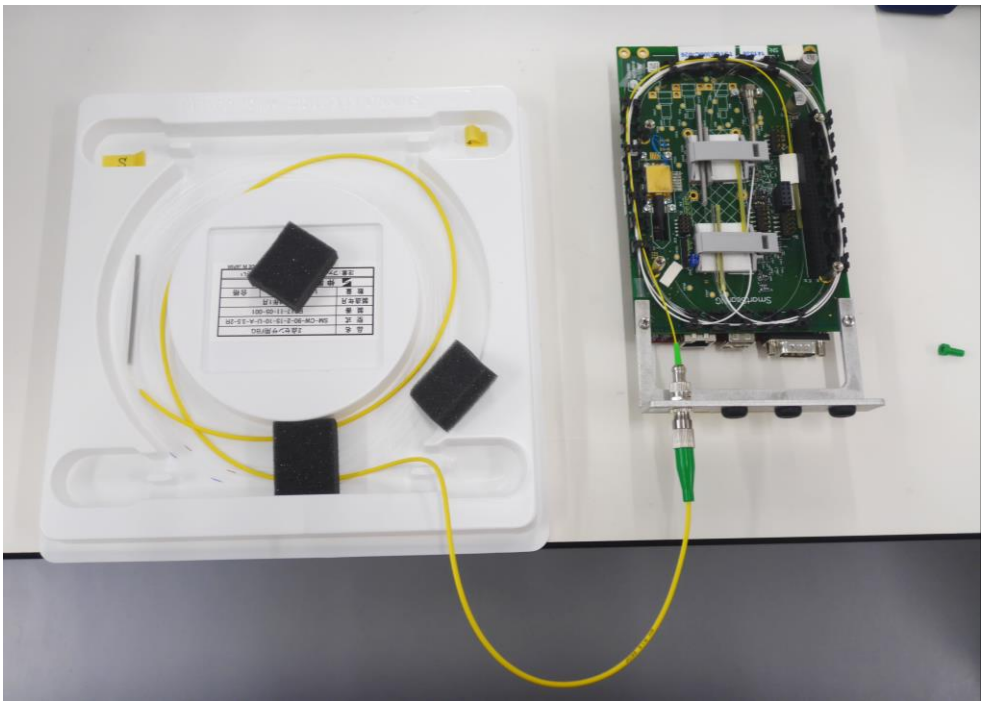


Figure 4-1 Over view of FBG sensor system

(smart scan SBI single Board Interrogator)

4.2.2 How to set the FBG sensor

Referring former study, FBG sensor is mainly attached on the wrist to obtain pulse wave signal. Wrist is brilliant point to detect pulse, on the other hand, it is difficult for adapt for sleeping person. Current FBG sensor system has to connect some interrogator which is not so small like watch. It is obvious that sleeping person moves hand recklessly. In order to prevent various accident, we first need to consider some point to attached the FBG sensor.

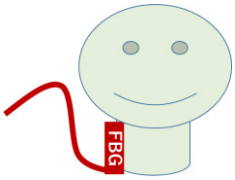
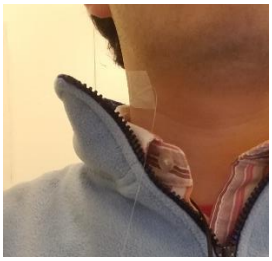
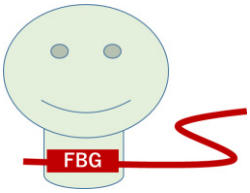
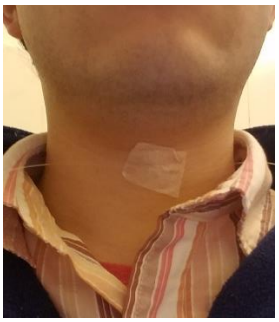
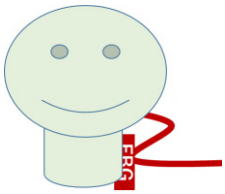
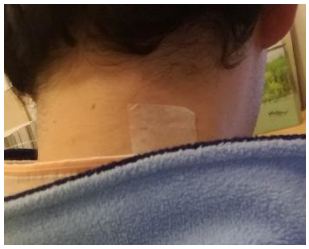
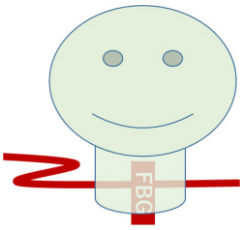
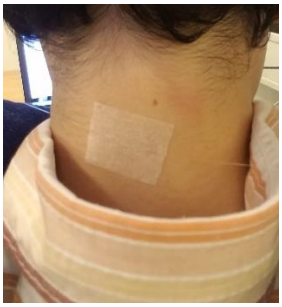
How to set the sensor was considered. Firstly, whether the sensor can get pulse wave signal or not was checked with one person. Measurement points are neck and pillow. Neck was the candidate for measurement point. Hence, by attaching FBG sensor several points where around neck, checked the what signal can sensor get. Subject is a twenties Male with sitting position. Sensor position are described below.

i. Right of neck
ii. Central of neck
iii. Diagonally left back of neck
iv. Back of neck

The detail of the sensing points is described below in Table 4-2.

Second plan, installing sensor on the pillow was considered like in Figure 4-2. In this case, it was difficult to decide the measurement points strictly. Just in case, we set 2 sensors on the pillow, canter of pillow and side of pillow.

Table 4-2 The detail of the sensing points

Sensing points	Illustrate of the sensing point	Picture of the sensing point
i. Right of neck		
ii. Central of neck		
iii. Diagonally right back of neck		
iv. Back of neck		

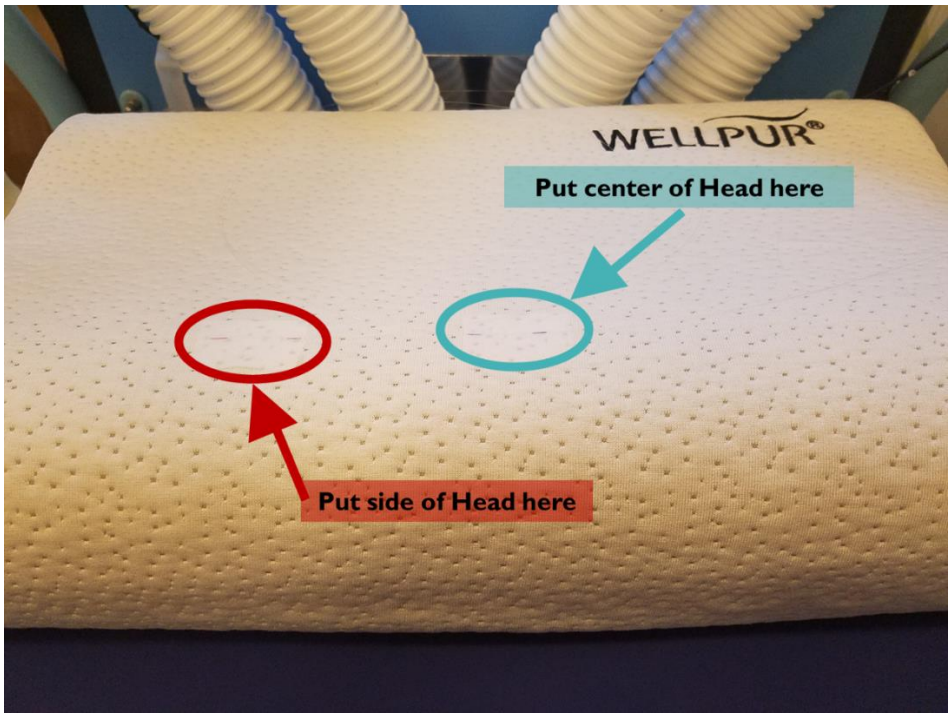


Figure 4-2 Location of sensor on the pillow

4.2.3 Experiment condition

In this study, we adopt the occipital region as sensing site. The FBG sensor was installed on the center of pillow by medical adhesive tape like in Figure 4-3. Due to its flexibility and high intrusiveness, the sensor is not felt by people uncomfortable and does not disturb sleep.

Four subjects (2 males and 2 females in their twenties) participated in the experiment. The experiment was performed in a climate chamber.

The subjects were lying in a bed for 2 hour and 50 min. All subjects participated over 3 days in experiments at room air temperature 15, 20, and 25°C. Respectively during the experiments the subjects were covered consequently with four different quilts for 30minutes. During this period, the FBG sensor get the signal from the occipital region. In total, experiment was conducted like showed in Figure 4-5, Scene of measurement is showed in Figure 4-4

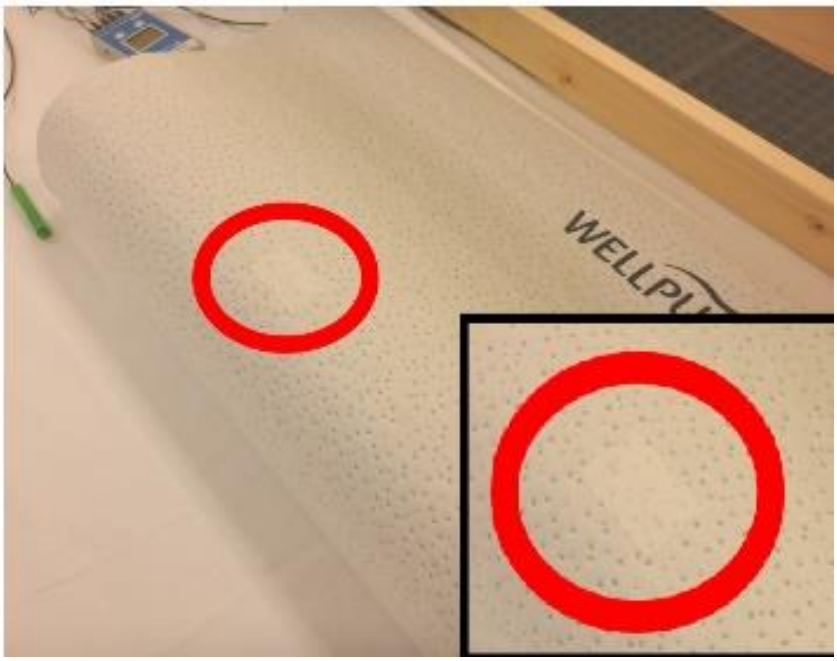


Figure 4-3 FBG sensor on the pillow.

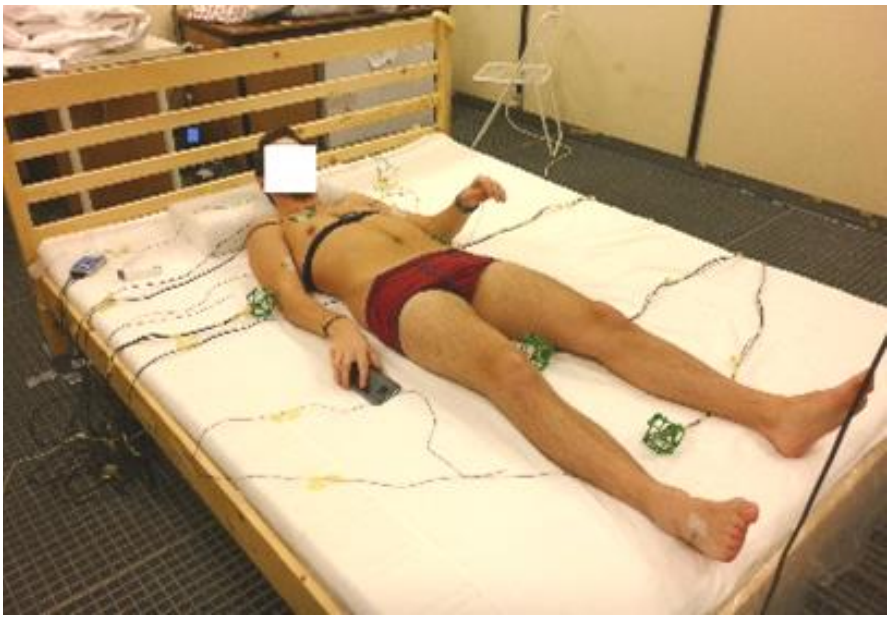


Figure 4-4 Scene of measurement

One Experimental Session (2 hour 50 min)

	Acclimatization	Break	Condition 1	Break	Condition 2	Break	Condition 3	Break	Condition 4
Time (min)	30 min	5	30 min	5	30 min	5	30 min	5	30 min
FBG measurement	-		3 times		3 times		3 times		3times

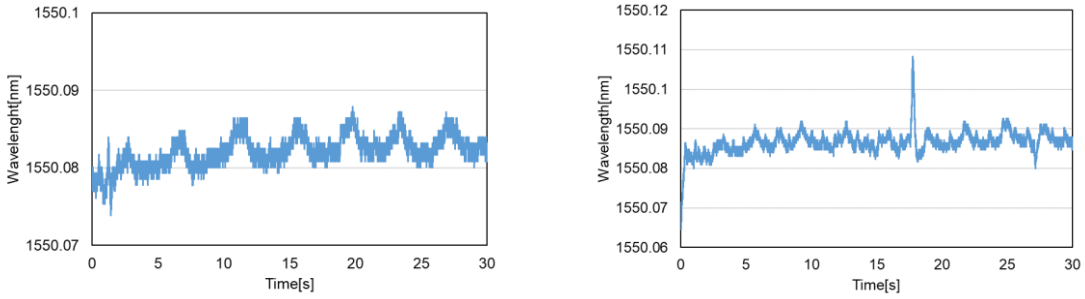
Figure 4-5 Experiments flow

4.3 Results

4.3.1 How to set the FBG sensor

Signals what sensor could get are shown in Figure 4-6, Figure 4-7, Figure 4-8, and Figure 4-9. We can see some peaks in Figure 4-6. We can guess there may be some information. About the Figure 4-7, there un-clear periodic peaks. Next, Figure 4-8 could not show clear signal, because the small amount of change. As same with former one, Figure 4-9 could not show the clear signal.

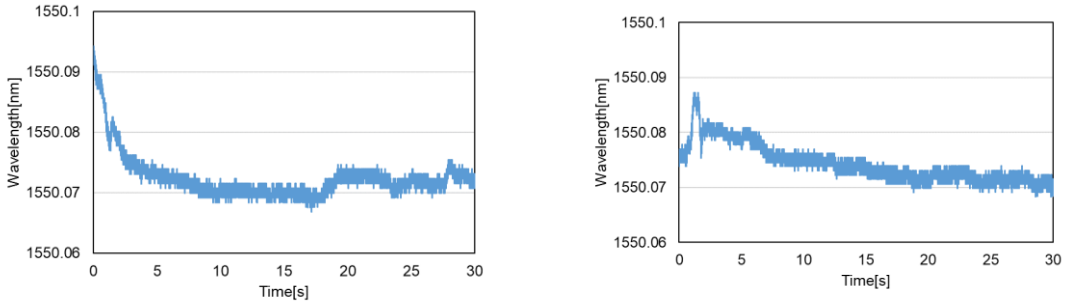
From these results, it can be concluded that the neck is not good points for measurement, because the vibration of blood vessel is not clear. Hence, it is considered there are not enough pressure against the neck is not enough to detect the vibrations.



(a) (b)

Figure 4-6 Signal from right of neck

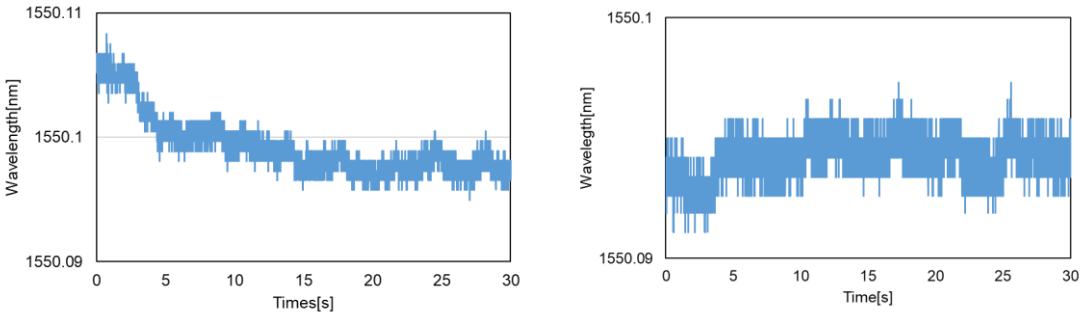
(a) measurement 1, (b) measurement 2.



(a) (b)

Figure 4-7 Signal from central of neck

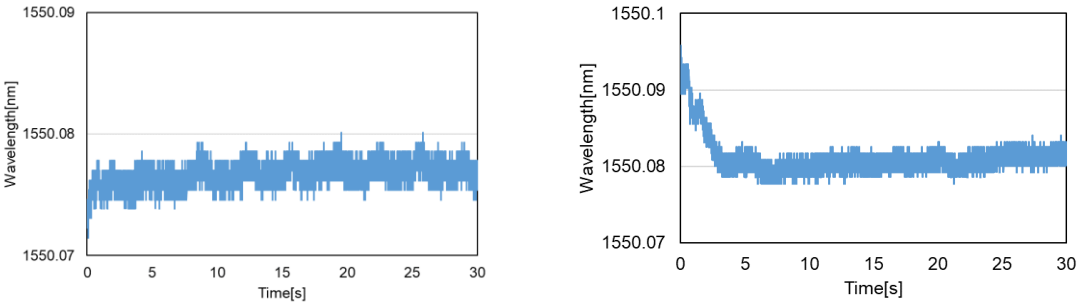
(a) measurement 1, (b) measurement 2.



(a) (b)

Figure 4-8 Signal from diagonally right back of neck

(a) measurement 1, (b) measurement 2.

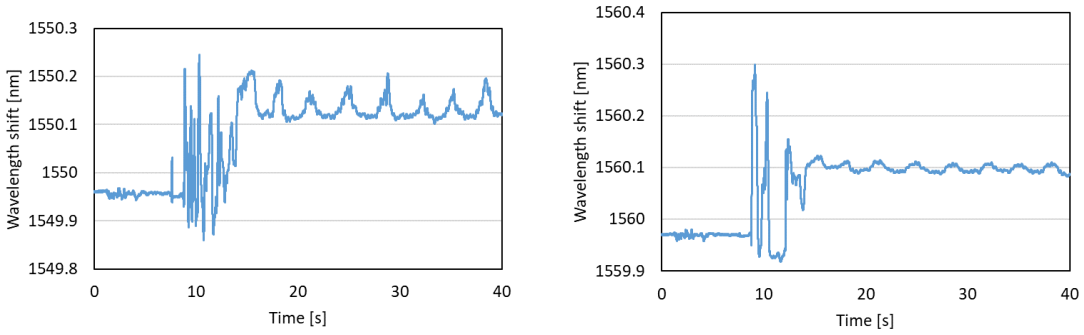


(a) (b)

Figure 4-9 Signal from back of neck

(a) measurement 1, (b) measurement 2.

As next strategy, the second plan was considered. Put the sensor on the pillow and press the sensor by subject's head. Much bigger pressure can be applied to sensor. Result is showed at the Figure 4-10. There are huge peaks which may drive from the body movements. On the other hands, there are clear periodic signal on the latter part. Compare with (a) and (b), (a) has the bigger amount of change in periodic peaks. That why, it can conclude the center of pillow is adequate to obtain signals from body.



(a) (b)

Figure 4-10 Signal from diagonally right back of neck
(a) from center of pillow, (b) from side of pillow.

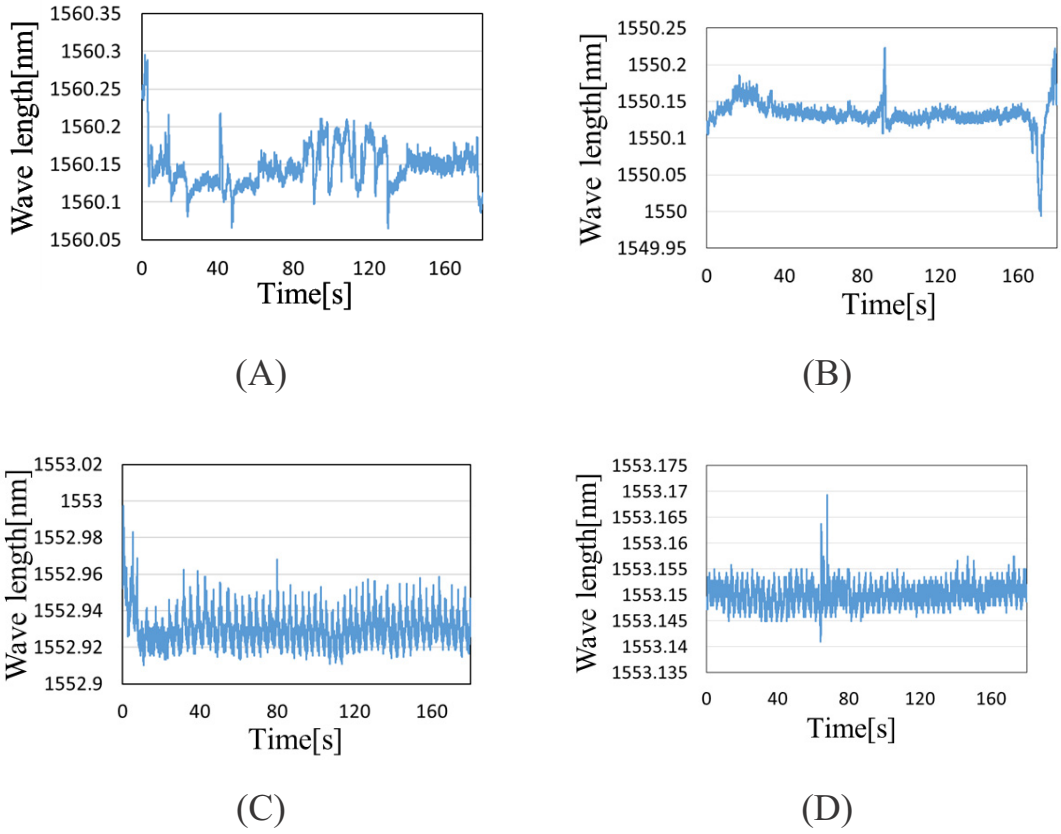


Figure 4-11 Scene of measurement, (A) from subject A, (B) from subject B, (C) from subject C, (D) from subject D.

4.3.2 The signal from the pillow

Figure 4-11 show the example of measurement from each subject with same condition. There are present the periodic peaks, those periodic peak are hidden by the huge drift of signal or bigger peaks. This means that the center of pillow is good points for taking up signals, and, there is also sensitive for body movements and noises. Bed-

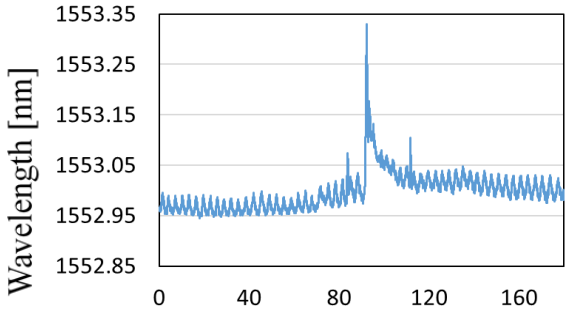
environment is totally different with sitting position or standing position, it can guess that the difficulties of measurement while sleeping.

4.4 Discussion

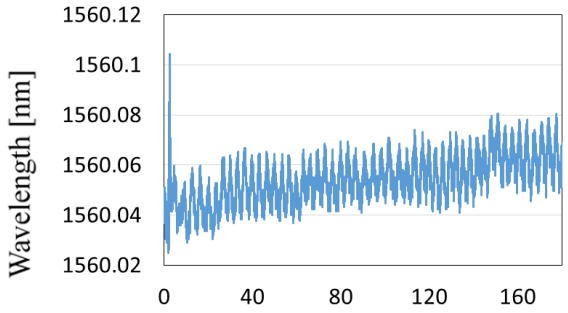
A lot of experiment conditions were prepared, however, there might not clear correspondence between signals and temperature, room temperature, exposure time, kind of quilts, nor day of schedule. Because, body movement was much dominative in this narrow area: head and pillow, rather than various parameters. Especially, measurement point was not visible, it was difficult to control and monitor.

Figure 4-12 show the typical 3 samples from all of measurement ignoring subject categories. All of measurement data are able to be classified with these 3 categories. Figure 4-12 (I.) sample is consisted from small parodic peaks and huge sharp peak. Figure 4-12 (II.) doesn't have huge peaks; entire signal is slightly drifting. Finally, Figure 4-12 (III.) show the extreme big amount of change: 0 to 1550 nm. It can easily guess that (I.) and (II.) may include some information of body. On the other hands, (III.) are dominated by huge amount of changes, not possible to taking up some

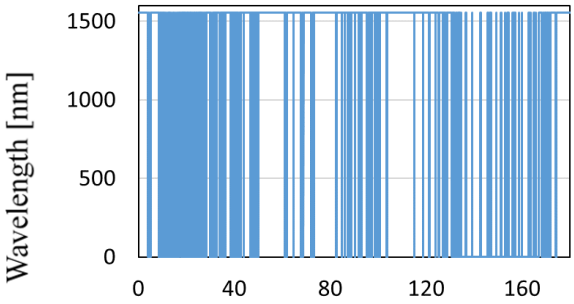
meaningful signals. This strange signal is occurred by the overweight against the sensor. Under the body, or quilts, sometimes FBG sensor got too much pressure and got bended, then lost the measurement function. In normal use, this never seen often, special condition; we can say it is bed-environment specific trouble. It can be stated that bed-environment does require the sensor which is neither just only high sensitivity, nor robustness.



I. Sample i



II. Sample ii



III. Sample iii

Figure 4-12 Representative three samples by classification

Focusing of details Figure 4-12 (I.), it is possible to find small periodic peaks like Figure 4-13. Then, Fast Fourier Transform (FFT) was applied for Figure 4-12 (I.) and (II.). Figure 4-14 show the signal after FFT. Strong peak around 0.3 Hz, the circled by red square, is considered as a frequency of inhalation and exhalation, this peak means the signal contain the information of breathing. Peaks around 1.1Hz, 2.2 Hz, and 3.3 Hz, the part rounded by red circle, can be considered as overtone of 1.1 Hz, corresponds the frequency of heart rate.

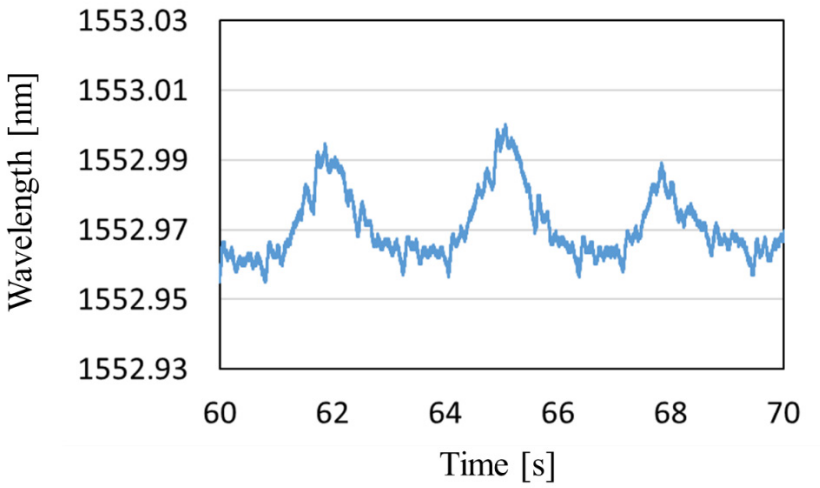
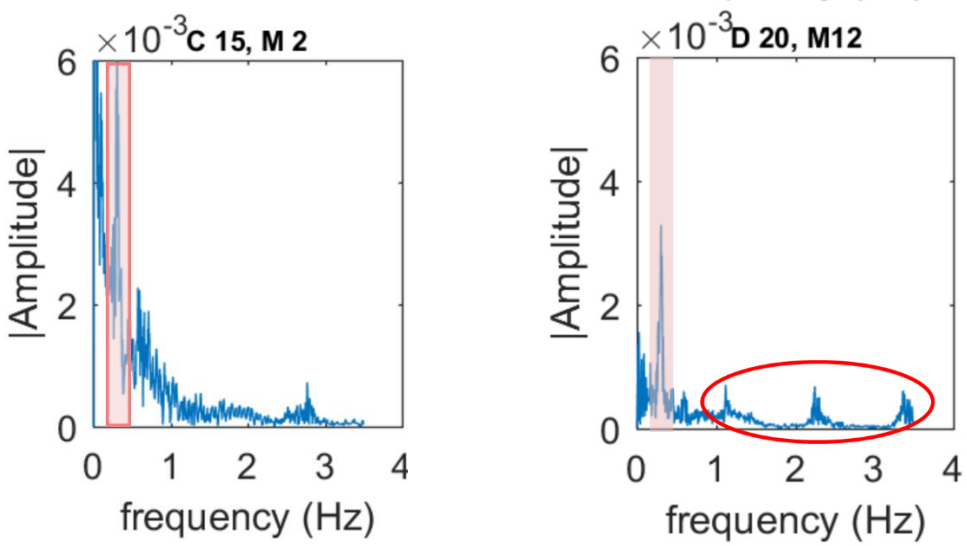


Figure 4-13 Detail of the signal "I. Sample i."



(P) (Q)

Figure 4-14 Representative three samples by classification

4.5 Conclusion and prospects

Tried to applied the FBG sensor to bed-environment for measurement vital signs. The point to measure and what the sensor measure were considered in this chapter. As a result, instead of attaching the sensor to the human body, it was founded that attaching the sensor on the center of pillow is better.

Taking this result, measurement was carried with 4 subjects. Measurement was got effected by bed-environment specific factors. However, some of signal show the periodic peaks which may be driven from body functions. Appling FFT, it was founded that those signals includes the information of breathing rate, heart rate and body movement.

It could be concluded that we can get the several vital signs from the pillow, even there is no direct contact with blood vessel and sensor. This result will help to improve the sleeping quality or detect disease in early phase. Moreover, the method also may be used for improving sleep quality, not only to develop functional pillow.

Currently, devices that measure the human body during sleep have appeared on the market. As shown in the figure below, there are devices that lay under sheets or the like and those that incorporate sensors in pillows like

in Figure 4-15. For these products, the FBG sensor system has an advantage in the high definition of the data that can be obtained. Those devices cannot measure blood pressure nor blood glucose level. Addition, there is no blood glucose level instrument which be possible to measure while sleeping. By progressing study of how to install the FBG sensor, we can make more functional product than those current devices.

Figure 4-15 Example of the marketed product (Nemuri scan)

Chapter 5
Development of active vital sign measurement system

Chapter 5
Development of active vital sign measurement system

5.1 Introduction

In order to helping aging society or daily Self-monitoring blood glucose (SMBG), we had been studied for developing wearable vital sign monitoring device. However, the measurement is decided, conducted, managed by their own. If miss the timing to measure, or forget to measure, measurement cannot achieve the role. With the elderly people or child, even if measurement can be performed with existing products, sometimes they cannot interpret with respect to the obtained values. When measuring various vital signs in hospitals and the like, an error factor so-called “white coat hypertension” may be included in the measurement.

Hence, we suggest the health managing with robot equipped vital sign sensor. This robot aims to approach like preventive medicine and support the measurement staff. Addition, robot is desired to record the measurement and urge the measurement, which traditional devices never

have done. Moreover, reducing the effect of white coat hypertension is also expected.

Towards the goal written above this chapter report the trial for assemble robot which has vital sign measurement function. The FBG sensor system, known as a multi-vital sign monitor device, is mounted on the fingers of a commercially available humanoid robot “Pepper”. We aimed to assemble the system which possible to calculate vital signs of four items of respiratory rate, pulse rate, systolic blood pressure, and diastolic blood pressure in about 20 seconds simply by touching the hand of the robot “Pepper”.

5.2 Material and methods

5.2.1 FBG sensor system Employing Optical Edge Filter: Satoshi

Interrogator has been used mechanism like an interferometer, it can conduct measurement with high stability. On the other hands, the machine box must be big, that was a problem, this time, the system aims to be installed to the robot, it is difficult to apply Mach-Zehnder interferometer, as well. Therefore, the "Wireless, Portable Fiber Bragg

Grating Interrogation System Employing Optical Edge Filter" which reported by K. Ogawa et al. [40] was adapted as mechanism, named “Satoshi”. This is developed to obtain vital sign more accuracy than current interrogator, entire system was got smaller by employing optical edge filter [2-3]. The comparison between the PF-20 (Nagano Keiki co. ltd.) which is previous interrogator and this interrogator; Satoshi is described below in Table 5-1.

Table 5-1 Size of interrogator

	PF20	Satoshi
Wide [mm]	214	74
Depth [mm]	262	97
Hight [mm]	90	57
Weight [g]	2800	175

5.2.2 Optical edge filter

The optical edge filter is one of optical components and is a kind of derivative thin film. It is applied to various products as a Wavelength

Division Multiplexing (WDM) filter and usually detects using the pass band and stop band [41].

However, this interrogator focused on the slope part [40] of the edge filter as shown in Figure 5-1, uses the property that the ratio of transmitted light and cut-off light changes depending on the wavelength. This time, two wavelength gradient filters with the same reflected / transmitted light intensity at 1543 nm and 1561 nm were used. Since the Bragg wavelength of the FBG sensor varies greatly depending on the fixed pressure, body temperature, and ambient temperature when affixed to the human body, the Bragg wavelength may not exist in the inclined region. Therefore, a wavelength gradient filter having a gradient region within the range of 1 nm was employed in this experiment. As a result, the change in Bragg wavelength returned from the FBG sensor can be calculated from the ratio of transmitted light and reflected light.

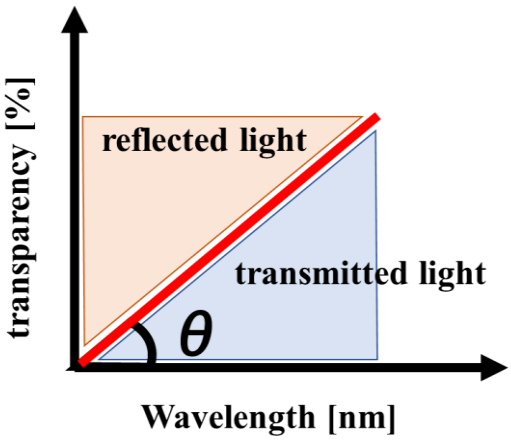


Figure 5-1 Wavelength characteristic line of Optical edge filter

5.2.3 Human shaped robot: Pepper

The humanoid robot used is Pepper made by Softbank robotics. In this research, Pepper for Biz, a product for enterprises, is adopted. This machine is characterized by being able to speak Japanese very smoothly, and is equipped with various sensors throughout the body so that it can run in the room without touching obstacles. In addition, it is possible to provide a height suitable for human's blood pressure measurement due to its high overall height, having 5 fingers, and to be able to present visual information with a tablet terminal on the chest, which is an advantage over other humanoid robots.

Owing to these features, this robot can perform active measurements and allow unlike previous vital sign measuring

instruments.

5.2.4 Vital sign calculating methods

In this study, the measurement target is pulse, respiratory rate, systolic blood pressure, and diastolic blood pressure. FBG sensor and multivariate analysis were used for calculation. It is known that an FBG sensor can measure several vital signs from a pulse shape by combining it with a pulsation point of a human body and combining analysis methods such as multivariate analysis. This step conducted by analyzing the obtained pulse wave and the reference value to construct a calibration curve. In this paper, various values are calculated using the calibration curve previously constructed using the FBG sensor. The calibration curve is constructed by 60 points of measurement data from a male in his 20s.

5.3 System Formation

The entire system is mainly composed of three components: FBG sensor system; Satoshi, Pepper, and server, like showed in Figure 5-2. FBG

sensor is installed on Pepper's right hand's index finger. This FBG sensor connect to the laptop computer via a wired LAN cable. The laptop is connected to the Internet via a mobile router and Wi-Fi. Information is stocked on the server, which Pepper can read it, and finally displays it as a measurement result on the chest tablet.

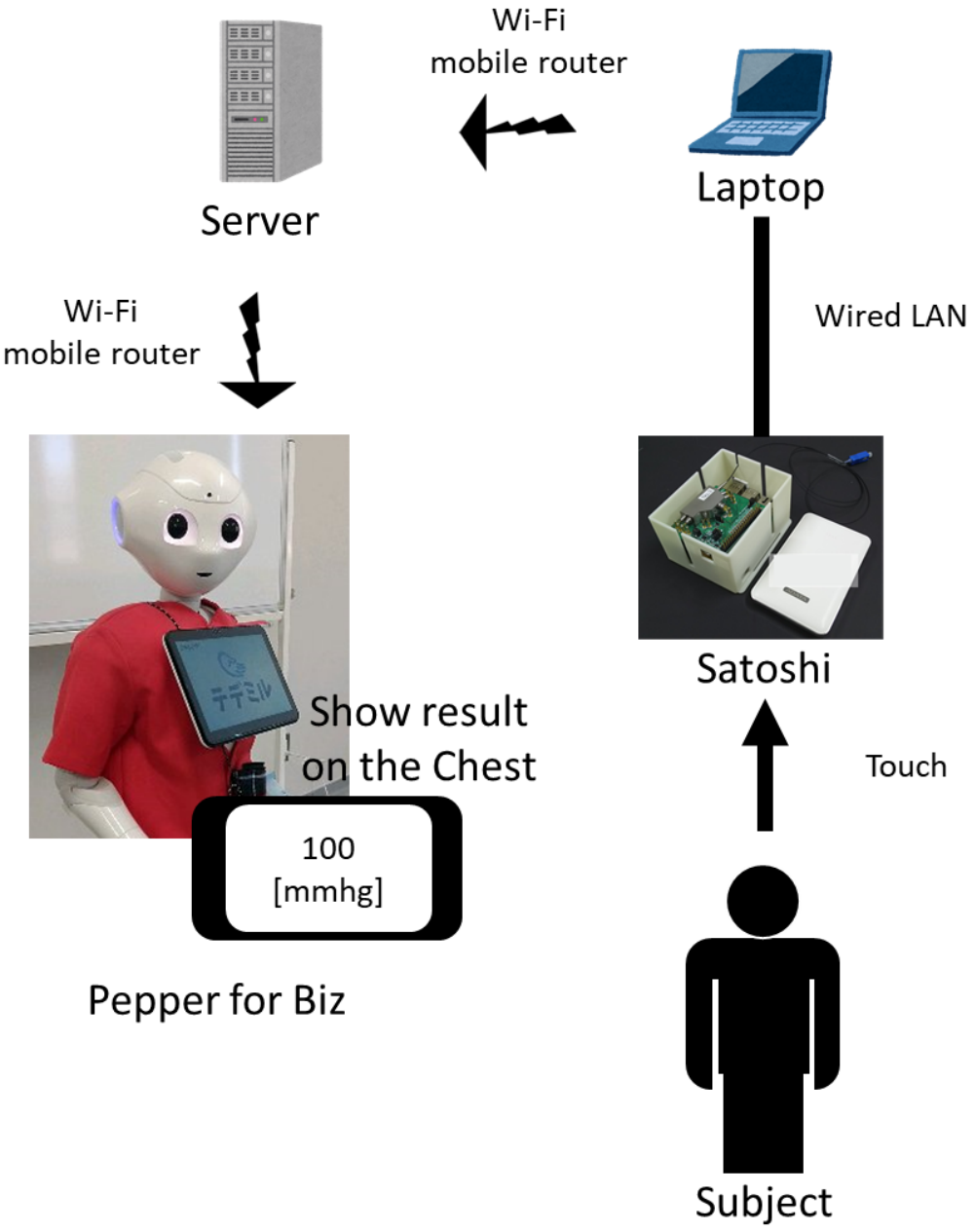
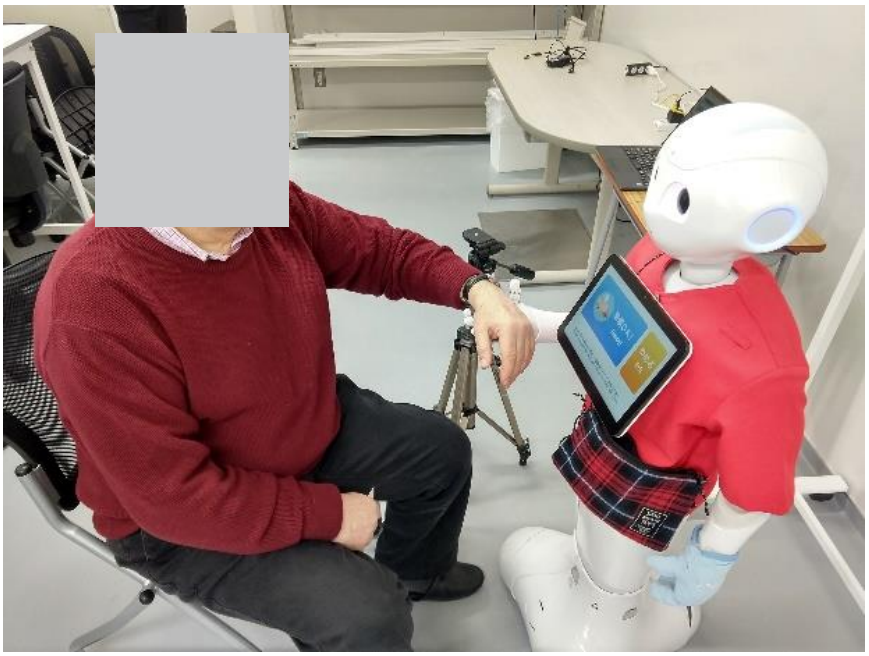


Figure 5-2 Data transition flow of entire system

5.3.1 Getting pulse wave signals

The FBG sensor system obtains a signal by touching the pulsation point of the human body. In this system, the pulsation point is defined as the left wrist. This is because, in many previous chapters and studies using the FBG sensor system, the calibration data used by the left wrist was also obtained from the left wrist.

As shown in the Figure 5-3, the subject conduct measurement facing the Pepper. The FBG sensor is adjusted to be close to the beat point of the person's left wrist.



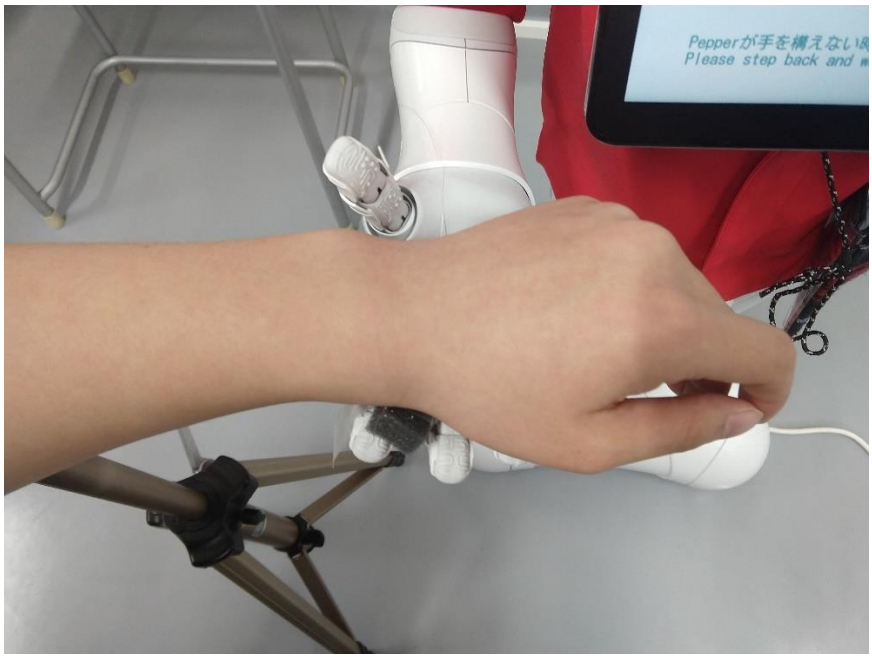


Figure 5-3 State during measurement

5.3.2 Pepper as a human interface

This system used the Pepper to guide the subject to use the FBG sensor system, to communicate data, and to show the results. It is set to pay close attention to the movement, so that it does not touch person himself, guides the subject to be measured, and guides the measurement and result report by voice, video, gesture. The behavior patterns are shown below in Figure 5-4.

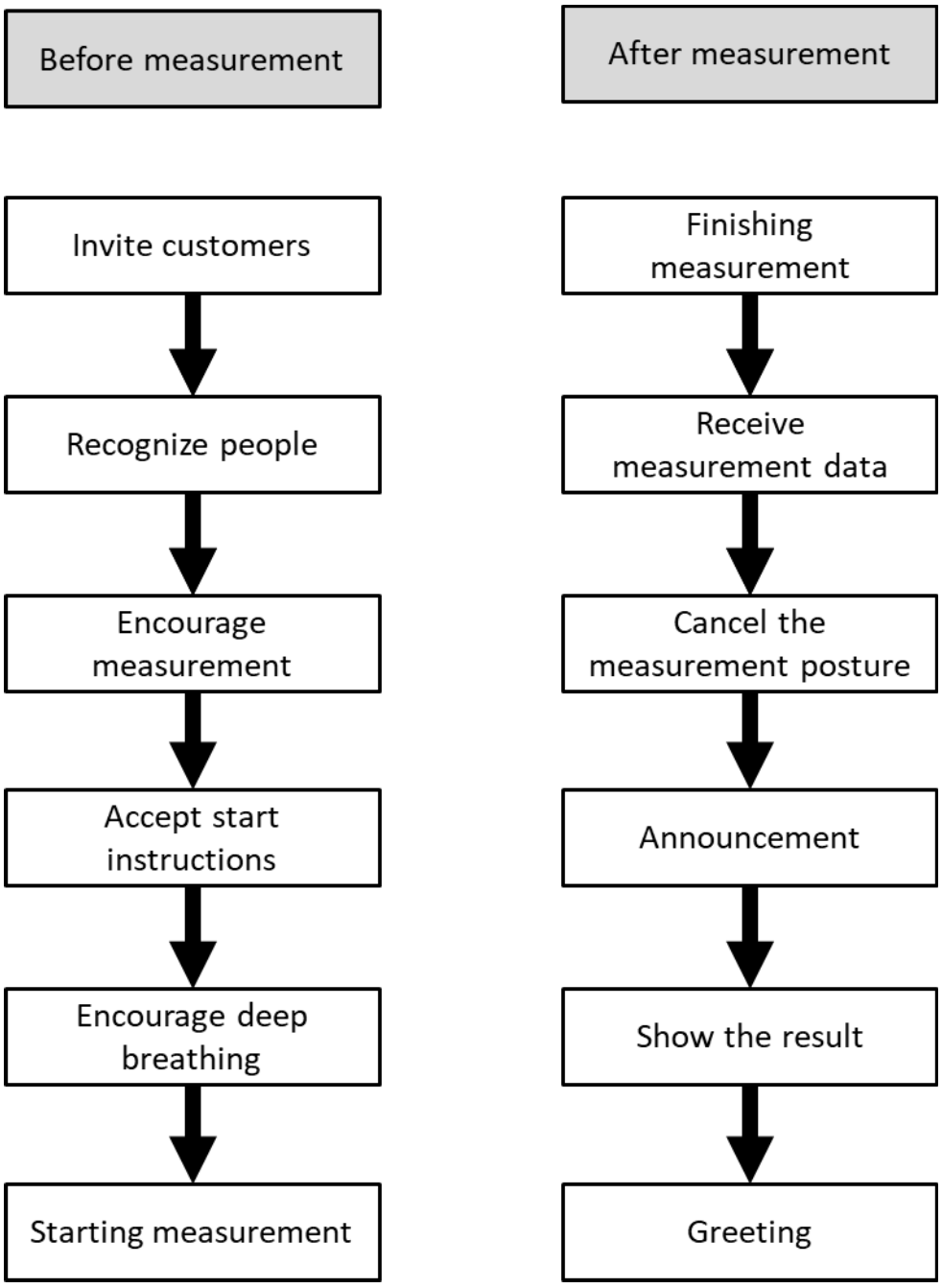


Figure 5-4 Flow of behavior for Pepper as a human interface

5.4 Measurement result and discussion

Table 5-2 below shows the results of measurement with this system installed. Measurements were made as much as possible with the explanation by Pepper, reducing human intervention. In addition, the subject was a person who visited randomly, and NaN in the composition table means measurement failure.

It is not possible to determine the authenticity of the value only from the main measurement result. However, there are obvious measurement failures such as pulse rate over 300 and number of breaths 0 in the table. In such a case, measurement of blood pressure often fails. Such measurement failure has never occurred with the other FBG sensor system and is a problem unique to this system. The failure of these measurements is due to the sensor part of the system not having good contact with the subject's pulsation point.

In order to improve this measurement, there is a primary need to refine Pepper's induction. Second, Pepper's fingers have no sensory function. Therefore, it is not possible to have a mechanism for detecting a pulsation point, and it is not possible to make a fine adjustment to change the measurement point subtly. In the future, it will be necessary to devise ways to supplement functions that do not exist in Pepper.

Table 5-2 Summary of measurement with system

Number of Measurement	Pulse Rate	Number of breath	Systolic blood pressure [mmHG]	Diastolic blood pressure [mmHG]
1	113	10	106	56
2	37	8	99	55
3	123	9	95	50
4	29	15	87	47
5	102	10	81	45
6	118	11	87	47
7	316	14	NaN	NaN
8	201	14	72	39
9	115	12	90	50
10	155	12	95	49
11	12	7	81	44
12	113	13	91	48
13	84	12	97	52
14	119	0	NaN	NaN
15	64	6	99	55
16	110	14	94	50
17	83	12	102	57
18	104	12	80	43
19	104	14	85	45
20	162	16	NaN	NaN

5.5 Conclusion and prospects

This system operated satisfactorily in the mobile router usable area. There was also no problem with continuous operation. As a result, in many subjects, this device was able to measure respiratory rate, pulse, and blood pressure. It can be said that the role as a prototype was fulfilled more than expected.

On the other hand, some of the elderly people got somewhat suspicious results. It was suggested that more stable measurement is possible by providing an interface and calibration according to the age of the person to be measured.

In future developments, we are considering using the functions installed in Pepper more satisfactorily as well as ensuring measurement accuracy. First, there is identification and identification of individuals by face recognition, and accumulation and tracking of individual measurement data. We believe that we can contribute not only to temporary vital sign measurement but also to tracking more than a certain period of time to pick up more information and early detection of serious diseases.

In addition, taking advantage of the characteristics of being always connected to the network, it is possible to transmit data obtained at home

nursing, etc., in order to provide remote medical treatment at a hospital. Schematic view of estimated future system is showed in Figure 5-5. This kind of personal identification and information management via the Internet can be expected to achieve the creation and installation of multiple units. In that case, we can expect a future where this machine can be provided and operated not only in nursing homes and hospitals, but also in hot bath facilities, pharmacies, and eventually in places where health care is required, such as schools and gyms.

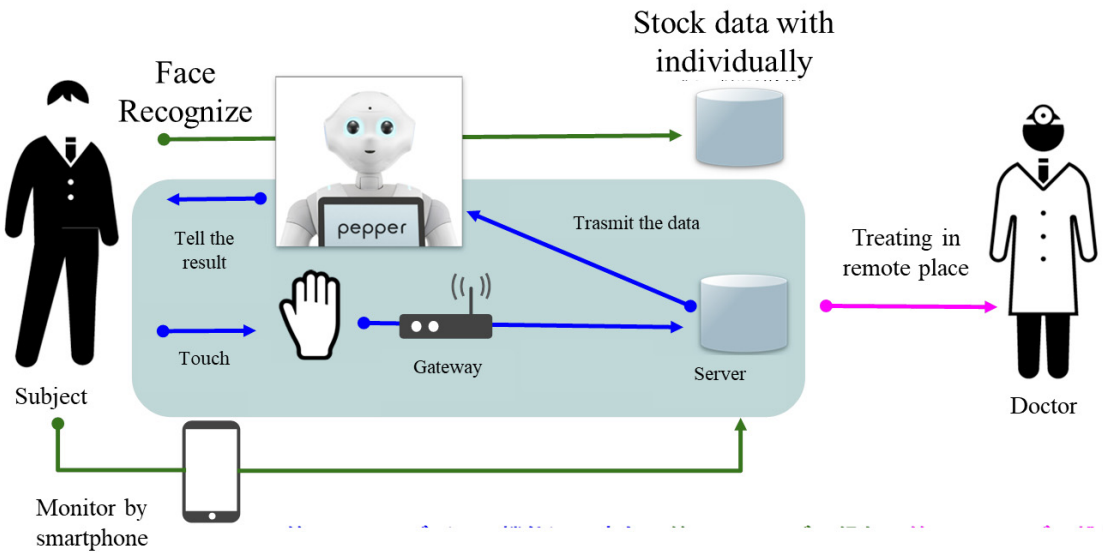


Figure 5-5 Under using system with subject

Chapter 6
Conclusion

Chapter 6
Conclusion

6.1 Conclusion

This dissertation considered how to measure blood glucose level and way of application FBG sensor system, in order to develop vital sign monitoring devices using optical fiber sensor.

Chapter 1 focused on the fact that aging society and increasing of diabetes. When the environment in aged society, it cannot avoid to lack of medical worker. Then, we proposed a preventive medical approach by monitoring various vital signs. Along with this, the present status of the vital sign measuring instrument and the advantages of this research using the FBG sensor system were described. On the other hand, since SMBG is indispensable for the treatment of diabetes, we mentioned the problems of current measurement instruments. In order to solve these problems, we described the aspect of the FBG sensor system as a non-invasive blood glucose monitor.

At chapter 2 and 3, the method to pick up the information of blood glucose level from pulse wave signal got from FBG sensor system was

discussed with two analyze way. As a result, it was found possible to measure blood glucose level with small error at healthy subject.

Chapter 4 explained about trial of introducing an FBG sensor system in a sleeping environment. We found the possibility of capturing the pulse and breathing during sleep without disturbing sleep and without installing it on the human body.

Chapter 5 described research on mounting FBG sensors on robots to construct a system that actively performs vital sign measurements. Study reached one stage, robot report was able to report the pulse rate, breathing rate, and blood pressure with about 30 seconds.

6.1 Prospect

The main purpose of this dissertation is to improve the quality of human life and medical care through vital sign monitoring technology. The FBG sensor system was proposed as the method, and the blood glucose level measurement method and the application method of the sensor system itself were sought. As a result, it was shown that blood glucose levels can be measured completely non-invasively and the FBG sensor system can be applied to a sleeping environment and installed on a robot. Therefore, a device capable of measuring not only blood pressure, pulse rate, respiratory rate, and stress but also blood glucose level can be provided. This makes it possible to check various vital signs without visiting a medical institution, in addition, since wireless communication is already possible, it is possible to transmit measurement data to a doctor and perform remote medical care. There is no need to bother a medical institution more than necessary. This enables early detection and early response by a medical institution when an abnormality occurs in vital signs. Thereby, it can contribute to efficiency improvement of medical care and reduction of medical expenses.

Furthermore, as mentioned earlier, this paper was able to measure blood glucose levels from pulse wave signals. As a result, it has been shown

that there is a possibility that it can be proposed as a new SMBG method if it has been developed and can be applied to everyone. Eventually, it will be a revolutionary approach among the current SMBG which is not to avoid bleeding. Ultimately, it will be a device that can provide blood glucose level and other signs while being always worn like a wristwatch or active measurement assistant.

Chapter 7
Appendix

Chapter 7
Appendix

7.1 Publication

The dissertation is based on the following published papers. I would like to express appreciation to two publishers.

- Shintaro Kurasawa, Shouhei Koyama, Hiroaki Ishizawa, Keisaku Fujimoto, Shun Chino, “Verification of Non-Invasive Blood Glucose Measurement Method Based on Pulse Wave Signal Detected by FBG Sensor System.” MDPI sensors, vol. 17, no. 12, Nov. 2017

- Shintaro Kurasawa, Hiroaki Ishizawa, Keisaku Fujimoto, Shun Chino, Shouhei Koyama. “Development of Smart Textiles for Self-Monitoring Blood Glucose by Using Optical Fiber Sensor.” Journal of Science and Technology, (Under review)

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