Recent advances of near infrared technology in the biomedical field

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Introduction

Over the recent years, biomedical applications of NIR spectroscopy[1–5] have received keen interest because of its many advantages, especially the non-contact and non-invasiveness, that allows an *in situ* analysis on various physical states, shapes and thicknesses of samples. As a good example of the recent advancement of NIR technology in biomedical fields, this paper presents an *in vivo* NIR study of non-invasive monitoring of blood glucose.

In vivo NIR non-invasive monitoring of blood glucose

We have been involved in non-invasive NIR blood glucose monitoring,[4–12] which is very much a challenging project because it deals with very weak signals of glucose directly from human skin, and the physiological conditions of skin tissue such as body temperature vary easily with time. Non-invasive blood glucose assay by NIR has been investigated extensively for many years.[1–19] Irrespective of these intensive studies, there is still no reliable NIR non-invasive blood glucose monitor at present.

One critical difficulty associated with *in vivo* blood glucose assay is an extremely low signal-to-noise ratio (S/N) of a glucose peak in an NIR spectrum of human skin tissue. We developed a new NIR spectrophotometer system with a set of two optical fibres to obtain the dermis spectra selectively. One set of optical fibres is attached to the skin surface vertically. The skin surface is illuminated by the measuring light through the inlet optical fibre, and the scattered light is collected by the detecting optical fibre. If one could choose an adequate fibre distance the penetration depth of the measuring light could be controlled. The light path property of this condition was confirmed by computer simulation based on a Monte Carlo method.[18]

Chemometrics is an essential tool for analyzing *in vivo* NIR spectra of human skin that show overlapping absorption bands.[20–23] The crucial point for building the best calibration models for the determination of blood glucose is to select the informative NIR regions where an optimised calibration model for glucose can be obtained. We developed several new chemometrics algorithms for wavelength interval selection and sample selection in multicomponent spectral analysis, such as moving window partial least squares regression (MWPLSR).[9,10,12,23] By using these wavelength selection methods, we could achieve a correlation coefficient and *RMSEV* of 0.9205 and 17.1924, respectively, for the non-invasive determination of blood glucose.

The NIR system for non-invasive blood glucose assay

Figure 1 depicts the NIR system that we developed.[6–8]

It consists of a tungsten halogen lamp (150 W), an optical fibre bundle, a switching device for selecting a light path, a flat field type grating, a 256 InGaAs photodiode array sensor extended to a cut-off 2100 nm, a 16 bit A/D converter and a signal processor. The actual optical fibre probe used for the system consists of one central detecting fibre and twelve illuminating fibres arranged in a circle [Figure 1 (b)]. The distance between the detecting optical fibre and each of the surrounding fibres is 0.65 mm. The diameter of the optical fibre probe is 9 mm. It is divided into two parts at the light source end, [Figure 1(a)] one part transmitting light to the reference site, and the other to the measurement site. The sensing end A-a is applied to the skin tissue and the sensing end B-a is connected to the standard reflectance target. We also calculated the light path and the light path length by simulating the light propagation in skin tissue. For this simulation a Monte Carlo method, which is adequate for strongly scattering media, such as human skin tissue, was chosen.[18]

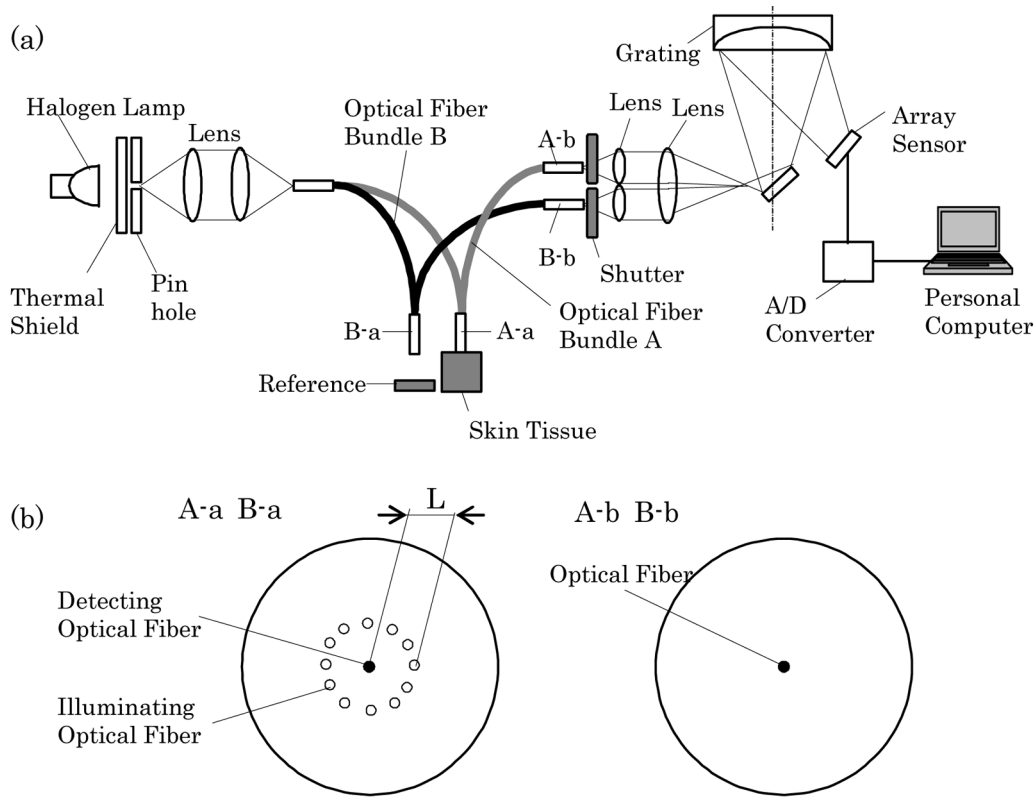

Figure 1. Schematic diagrams of (a) the instrument developed by our group, (b) the cross section of the probe developed. [Reproduced from Reference 6 with permission. Copyright (2003) IEEE.]

Diffuse reflectance NIR spectra of human skin

Figure 2 shows 50 diffuse reflectance (DR) NIR spectra of the forearm skin of one subject measured during one oral glucose intake experiment.[6]

Weak features arising from blood glucose, proteins, lipids and other substances in the skin were masked by the 1450-nm water band. This sharp absorbance peak at 1450 nm suggests that our system using the novel fibre probe can reduce interference from absorption by the stratum corneum.

Application of new chemometrics algorithms for wavelength interval selection to *in vivo* NIR spectroscopic determination of blood glucose

We developed several new chemometrics algorithms for wavelength interval selection in multicomponent spectral analysis for *in vivo* NIR determination of blood glucose.[9–12] They are MWPLSR,

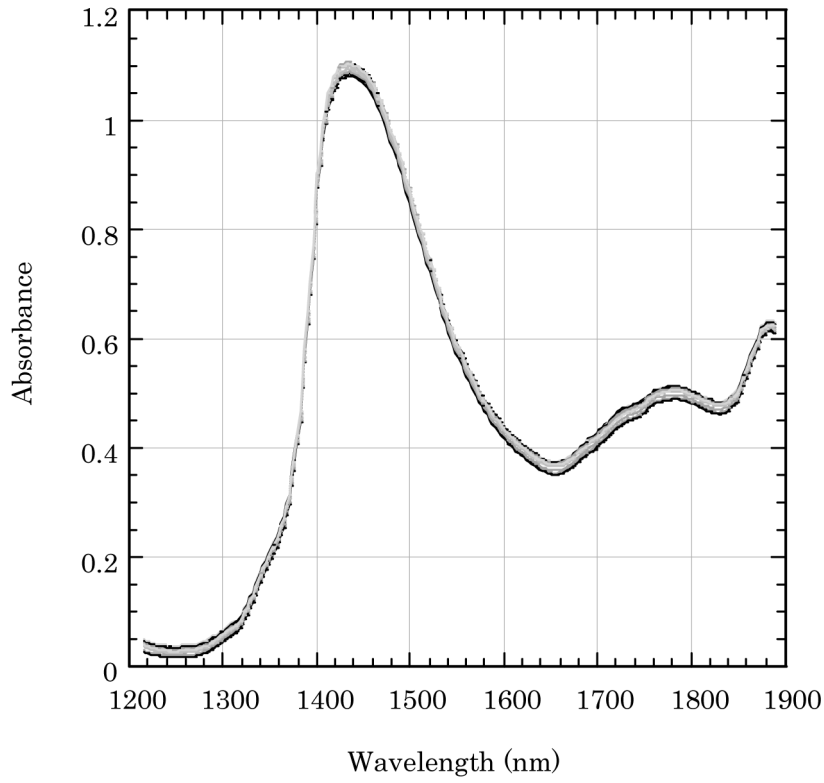

Figure 2. Fifty NIR spectra of the forearm human skin of one subject measured during one oral glucose intake experiment. [Reproduced from Reference 6 with permission. Copyright (2003) IEEE.]

Changeable Size MWPLSR (CSMWPLS) and Searching Combination MWPLSR (SCMWPLS). The goal of MWPLSR is to search for informative spectral regions for the multi-component spectral analysis. The informative regions contain useful information for PLS model building, and are helpful in improving the performance of the model. In MWPLSR, a series of PLS models are built for every window that moves over the whole spectral region, and then informative regions, in terms of the least complex of PLS models that reach the desired error level are identified.

Our proposed method is to use MWPLSR first to identify informative regions from spectra of a system like human skin. Next the optimised sub-region is searched for each selected informative region by CSMWPLS, or is directly searched for the optimised combination of regions by SCMWPLS.

We applied MWPLSR and SCMWPLS to the blood glucose assay (50–180 mg/dl) by *in vivo* NIR spectra of human skin.[12] We compared statistical results of blood glucose models built by use of the whole region, the individual informative regions, their direct combinations, and the optimised informative region. The PLS calibration model developed by using the whole region of 1212–1889 nm yields the large *RMSEV* of 20.1977 mg/dl with a high PLS factor of 7 and the correlation coefficient of 0.8936. The PLS calibration model based on SCMWPLS using the best optimised informative region of 1616–1733 nm yielded the best validation results, with the highest correlation coefficient of 0.9205 and the lowest *RMSEV* of 17.1924 mg/dl, with the PLS factor 4.

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