Mini review

Near-infrared spectroscopy: Promising diagnostic tool for viral infections

Akikazu Sakudo [a], Yoshikazu Suganuma [a], Takanori Kobayashi [a,b], Takashi Onodera [c], Kazuyoshi Ikuta [a,*]

[a] *Department of Virology, Center for Infectious Disease Control, Research Institute for Microbial Diseases, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan*
[b] *Sakai Bio-Clinical Laboratory, Inc., Shinkanaoka, Sakai, Osaka 591-8021, Japan*
[c] *Department of Molecular Immunology, School of Agricultural and Life Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan*

Abstract

Although several methods, including enzyme-linked immunosorbent assay, polymerase chain reaction, immunofluorescent assay, and Western blotting, have been used for the diagnosis of viral infections, none of them is ideal in terms of cost-effectiveness, speed, and accuracy. Currently, the rate of outbreak of emerging viruses is increasing and therefore the development and establishment of analytical methods for such viral infections are becoming more important. Near-infrared (NIR) spectroscopy is a fast, multicomponent assay that enables non-invasive, non-destructive analysis. Recently, the diagnosis of viral infections using NIR spectroscopy has been attempted. In this review, the potential of the NIR method in the medical and virological fields is discussed.
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Recently, the emergence of previously unrecognized viruses and re-emergence of known viruses which had been under control have been increasingly reported [1]. Global health has been threatened by recent outbreaks of emerging viruses such as severe acute respiratory syndrome-associated coronavirus [2–4], influenza A strains H5N1 and H9N2 [5], West Nile virus [6], human metapneumovirus [7], Ebola virus [8], and hantaviruses [9]. Emerging diseases also include variant Creutzfeldt–Jacob disease (vCJD) [10], *Escherichia coli* O157 [11], and human sleeping sickness [12]. It should be noted that 75% of human emerging diseases are zoonotic, i.e., they are caused by pathogens that are transmitted from animals to humans [13]. To prevent the threat of emerging infectious diseases, the Center for Disease Control and Prevention (CDC) suggests four strategies: (i) surveillance and response, (ii) applied research, (iii) prevention and control, and (iv) infrastructure [14].

Especially, applied research is important, because prompt detection and monitoring of emerging pathogens is enhanced by the development of analytical methods and helps to strengthen the public health infrastructure, ensure prompt prevention, and enable accurate risk assessment. Although various methods such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) are usually used for the detection of viral infections, those methods are not suitable for the large-scale routine screening that is required for surveillance. The development of an accurate, fast, and low-cost method of analysis of viral infections is needed. Near-infrared (NIR) spectroscopy is a fast, multicomponent assay that requires no sample preparation and no reagents [15]. Moreover, as water shows relatively weak absorption in the NIR region and NIR radiation is relatively low energy, NIR spectroscopy enables non-invasive analysis [15]. Therefore, NIR spectroscopy has become a widely used analytical method in the agricultural, pharmaceutical, chemical, medical, and petrochemical industries [16]. However, until very recently NIR spectroscopy had not been used in the virological

* Corresponding author. Fax: +81 6 6879 8310.
  E-mail address: ikuta@biken.osaka-u.ac.jp (K. Ikuta).

field. Recently, the diagnosis of viral infection using NIR spectroscopy has been attempted [17]. In this review, we introduce recent developments in NIR studies, the potential of NIR spectroscopy for rapid diagnosis of diseases and viral infections, and future prospects of NIR spectroscopy in the medical and virological fields.

Recent developments and problems in the diagnosis of viral infections

Early and sensitive detection of viral infection is necessary for the maintenance of a safe blood supply, treatment of viral infections, and prevention of transmission. The risk of transfusion-related transmission of viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell lymphotropic virus (HTLV) has been reduced by the development of sensitive serological tests for virus antigens and antibodies to viruses [18]. However, the risk of viral infections such as viral infection that is still in the pre-seroconversion window period, infection with immunovariant viruses, and infection consisting of immunosilent carriage still remains [19–23]. Several methods such as ELISA and PCR have been used for the detection of viruses from individuals during the pre-seroconversion window period. ELISA is commercially available, reliable, and specific. However, ELISA covers only a narrow range of virus antigens, and is time-consuming and expensive [24]. PCR is sequence-specific. The sensitivity of PCR is several orders of magnitude higher than those of conventional serological tests [25–27]. However, PCR may be not suitable for large-scale routine screening [28]. To reduce the cost of PCR, pooled plasma has been used to screen large numbers of samples, but the pooling method reduces the sensitivity to the same level as that of ELISA [29]. To concentrate virus particles, ultracentrifugation has been used, but ultracentrifugation causes a high rate of false-positive results [30]. Furthermore, a high rate of false-positive results [30] and false-negative results due to the mismatch of the primers for subtypes of viruses [31] has also been reported for the PCR method. Moreover, particular precautions are required to avoid cross-contamination in PCR analyses. Recently, multiplex PCR assays for viruses have been developed [32,33]. That method is slightly improved in terms of cost-effectiveness and time, but does not address the other limitations of PCR. Thus, the development of an accurate, fast, and low-cost method for the diagnosis of viruses based on novel concepts is needed.

NIR spectroscopy

NIR spectroscopy is the spectroscopic method using NIR radiation, which covers the region of 700–2500 nm. NIR spectroscopy was first applied for measuring the moisture content in grain and seeds [34]. Within the NIR region and the red region, 650–1000 nm, called the "optical window," is the most useful region for analyzing biological samples, because the overwhelming absorption of hemoglobin and water below 650 nm and above 1000 nm, respectively, limits spectroscopic and microscopic studies in these regions [35]. Use of the 650–1000 nm region enables us to analyze the changes of several molecules besides water and hemoglobin in animals in vivo. It is known that several compounds that exist in tissues show absorption in the NIR region and are present in sufficient quantities to affect transmitted NIR radiation. The absorption of molecules in the NIR region is due to combinations and overtones of vibration such as stretching and bending of hydrogen-bearing functional groups such as -CH, -OH, and -NH [36]. Water, melanin, and bilirubin in animals and chlorophyll in plants absorb NIR radiation, although the levels of these molecules remain constant with time [35]. In addition, oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and oxidized cytochrome c oxidase have characteristic absorption spectra in the NIR region [37]. Recently, biologically important molecules have been investigated by NIR spectroscopy [15]. The diagnostic potential of NIR spectroscopy has been recognized since Jöbsis first demonstrated oxygenation in cats by NIR spectroscopy [38]. NIR spectroscopy has also been used for diagnosis in a broad range of clinical applications [15].

NIR spectroscopy is a secondary method requiring calibration for the constituent of interest [39]. For example, calibration of NIR spectra to measure an object such as a virus compositional property or quality of virus depends on a multivariate mathematical modeling process based on a set of reference data which have been obtained by a standard chemical method. The process of calibration and its subsequent validation are an important part of NIR analysis. Schematic diagrams of the NIR calibration procedure are shown in Fig. 1(a). Samples for the calibration set should be obtained in a similar way to those that will be analyzed in the future. Uniformity of the solvent among samples is important. Especially, in blood samples, identical methods of preparation of plasma and serum are necessary. Furthermore, calibration of samples with a wide range in composition of not only the property of interest but also of all possible sources of variation likely to be encountered in the future is desirable. Stable humidity and temperature should be maintained during the scanning event, because humidity and temperature may affect water absorption in the NIR region. In the case of in vivo analysis of living organisms, the effect of temperature on the NIR spectra of living organisms may be less than that on the spectra of samples in solution, because the temperature of living organisms is stable.

The current diagnostic methods used for viral infection, such as: (i) serologic assays, which detect antibodies to virus, (ii) virus antigen detection by ELISA, and (iii) nucleic acid detection for viral DNA and RNA by PCR, are all expensive and time-consuming. NIR spectroscopy is non-invasive and rapid (less than 1 min from sample introduction to virus antigen value) and requires

no reagents for the analysis. Furthermore, NIR spectroscopy can simultaneously measure many components. Therefore, NIR spectroscopy has great potential as a routine diagnostic method for viral infection. If the NIR spectroscopy apparatus is automated, the rapidity can be further increased.

Future prospects of NIR spectroscopy

Most of the work done during the past 30 years on NIR in the medical field was based on oxygenated or deoxygenated hemoglobin. That work has been widely used not only for diagnosis of diseases but also functional analyses of brain and muscle. This is because NIR radiation is relatively transmittable in the NIR region. The characteristics of NIR radiation enable non-destructive and non-invasive analysis in vivo. However, in spite of being an appropriate method for the diagnosis of viral infection, NIR spectroscopy has hardly been used in the field of virology [17]. The value of NIR spectroscopy as a research tool is only beginning to be realized. The future should see increasing use of NIR spectroscopy in the field of virology for diagnosis, routine analysis, and laboratory tests to detect viral infection, characterization of viruses, examination of the pathology of virus-associated disease, measurement of virus load, and so on. Furthermore, as NIR spectroscopy
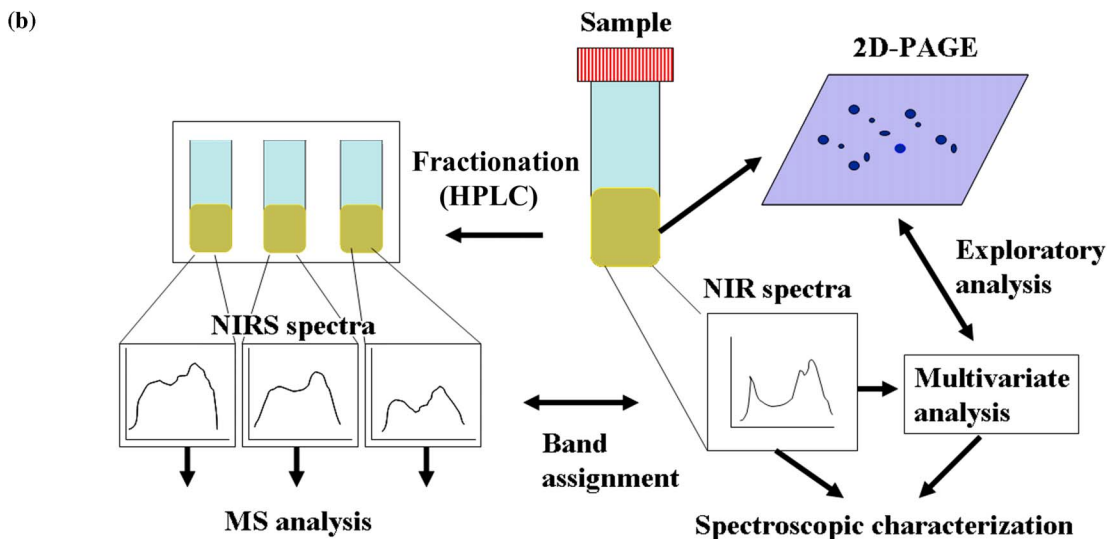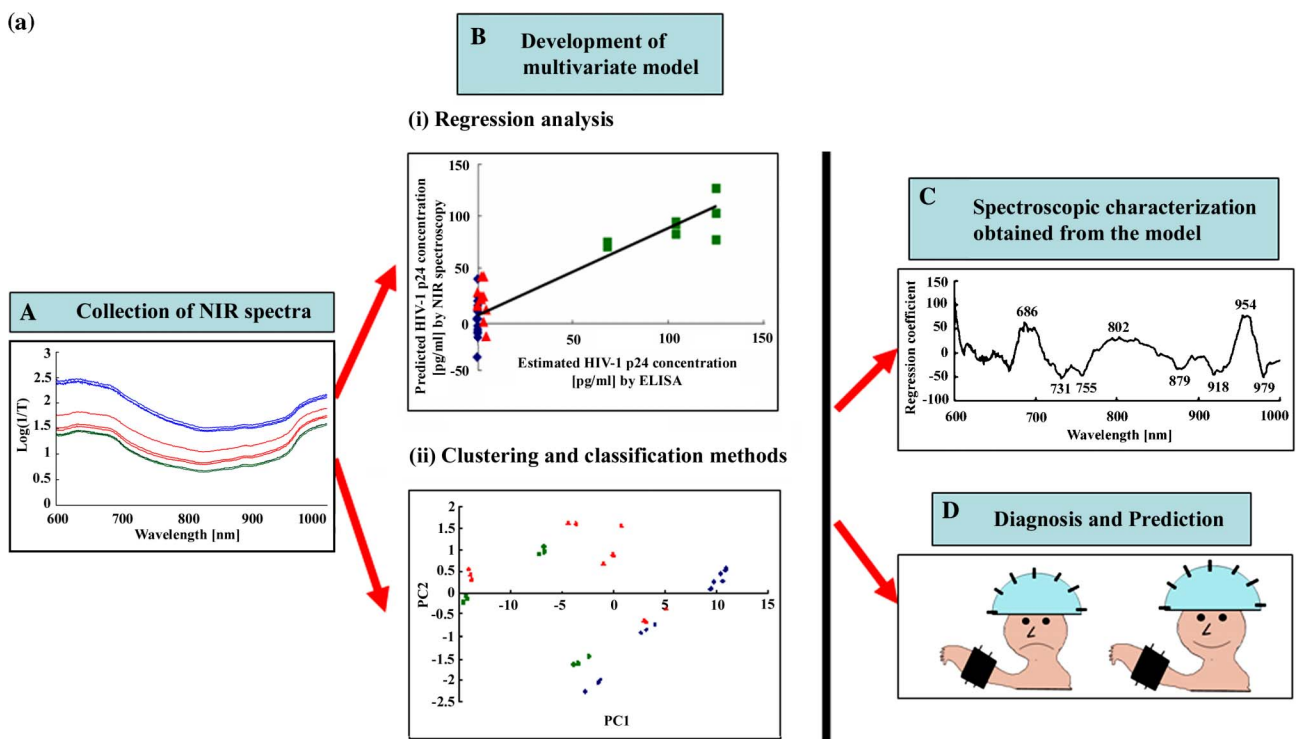
is suitable for in vivo analysis, NIR spectroscopy may be applicable for pre-mortem assays for prion diseases such as bovine spongiform encephalopathy (BSE) and CJD [40].

Multivariate analyses such as partial least-squares regression analysis (PLS), principal component regression analysis (PCRA), principal component analyses (PCA), and soft independent modeling of class analogy (SIMCA) are the most useful methods for analyzing NIR spectra [41]. We suggest that NIR spectroscopy when coupled with chemometrics constitutes a powerful approach for characterizing biomolecules and testing for diagnostic purposes. One important consequence of the development of NIR spectroscopy has been the realization of the importance of accurate band assignment. One commonly used band assignment method is replacement of isotope. For example, band assignment of water is carried out by comparison of the NIR spectrum of water (H_2O) with that of D_2O [42]. However, this method cannot be applied for most biomolecules such as proteins, lipids, and sugars, because the band assignment of such biomolecules is difficult due to the complexities of these hydrogen-bearing molecules. Some studies attempted to use NIR spectroscopy to predict the concentration of recombinant proteins [43], but there have been few such endeavors. This is because the absorption of minor constituents such as recombinant proteins may be easily overwhelmed by more intense bands from other matrix components such as solvent. Therefore, specific absorption for the recombinant proteins only appears to be obtained at concentrations of 5 µg/ml and above, which is considerably higher than the concentration observed in living organisms. If band assignment using fractionated biomolecules were possible, the applications of NIR spectroscopy would be greatly expanded. The key problem is that the absorption of biomolecules in the NIR region is very low, and the absorption bands are overlapping and interacting. To overcome these problems of NIR spectroscopy, the use of NIR fluorescent dye-labeled probes or solvent may increase the sensitivity and specificity, and give rise to a linear relationship between biomolecule concentration and signal. Furthermore, recently, a highly sensitive detection method for NIR spectroscopy has been developed. This method based on absorption-sensitive surface plasmon resonance achieved ~100 times enhancement of absorbance [44].

The use of the combination of NIR spectra and multivariate analysis is a totally exploratory approach. For example, by using NIR spectroscopy coupled with PCA, we can easily and rapidly obtain outlines of the samples and assess fundamental differences. Furthermore, discrimination of spectroscopic clusters by qualitative analyses such as PCA and SIMCA, and quantification of biomolecules by quantitative analyses such as PLS and PCRA may be further strengthened by traditional proteomics tools such as high-performance liquid chromatography (HPLC), two-dimensional gel electrophoresis (2D-PAGE), and mass spectrometry (MS) analysis (Fig. 1(b)). HPLC separates biomolecules. 2D-PAGE is used for exploratory analysis to delineate the differences of expressed proteins among samples. MS is used for identification of proteins.

Fig. 1. (a) NIR calibration flowchart for viral infections. The process for establishing an NIR calibration model for viral infections is shown. Samples from healthy donors and individuals infected with virus are subjected to analyses by the reference method and NIR spectroscopy. After the collection of NIR spectra, the spectral data are pre-processed and subjected to quantitative or qualitative calibration modeling to develop a multivariate model to evaluate viral infection or virus load, which is measured by the reference method. For the development of a quantitative model, regression analyses such as partial least-squares regression analysis (PLS) and principal component regression analysis (PCRA) are used. For the qualitative model, clustering, and classification methods such as principal component analyses (PCA) and soft independent modeling of class analogy (SIMCA) are used. The model is confirmed by validation methods such as leave-out cross-validation. If the model is not acceptable, re-calibration is performed after the validation. The NIR model can be used for spectroscopic characterization of viruses as well as diagnostic tests of viral infection. Spectroscopic characterization is discussed from the model based on the NIR spectra of samples from virus-infected individuals and healthy donors. (A) Three consecutive spectra of plasma samples from an HIV-1-infected individual [red lines: HIV-1 p24 ELISA (−), HIV-1 PCR (+); green lines: HIV-1 p24 ELISA (+), HIV-1 PCR (+)] and a healthy donor (blue lines). (B) (i) PLS calibration model for estimating the HIV-1 p24 concentration of 12 subjects. Cross-validation model: 7 PLS factors based on the 600–1000 nm spectral region; $R = 0.8555$, standard error of cross-validation (SECV) = 23.33 pg/ml, standard deviation (SD) = 43.30 pg/ml, SD/SECV = 1.856 using a leave-out cross-validation procedure for HIV-1-infected individuals [red triangles: HIV-1 p24 ELISA (−), HIV-1 PCR (+); green diamonds: HIV-1 p24 ELISA (+), HIV-1 PCR (+)] and healthy donors (blue squares). (ii) PCA (first two principal components) for 12 subjects. PCA score plot of first principal component (PC1) versus second principal component (PC2) for plasma from HIV-1-infected individuals [red triangles: HIV-1 p24 ELISA (−), HIV-1 PCR (+); green diamonds: HIV-1 p24 ELISA (+), HIV-1 PCR (+)] and healthy donors (blue squares). (C) Regression coefficient for the model based on the spectra in the 600–1000 nm region of plasma from HIV-1-infected individuals and healthy donors shown in (B) (i). (D) After development of the model, NIR spectroscopy is rapid and requires no reagents for the analysis. Moreover, in principle, NIR spectroscopy can be used for the detection of viral infections in target cells, animals, and individuals after development of the model calculated from the spectra of virus-infected and non-infected cells, animals, and individuals. Thus, further study is necessary to establish an NIR model for various viral infections in various types of samples as another additional method of analysis in addition to ELISA and PCR. NIR spectroscopy may be also applied for diagnosis of infections by other viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus (HTLV), and emerging viruses. If NIR spectroscopy proves to be able to sensitively discriminate different viral infections, NIR spectroscopy would become a promising diagnostic tool for addressing the issues of blood supply safety and emerging virus outbreaks. Modified from Figs. 2, 3, and 5 in Sakudo et al. [17] with permission from Center for Academic Publications Japan. (b) NIR spectroscopy coupled with proteomics may provide a powerful exploratory tool. High-performance liquid chromatography (HPLC), two-dimensional electrophoresis (2D-PAGE), and mass spectrometry (MS) constitute traditional analytical tools in classical proteomics. Samples are fractionated by HPLC using several columns. 2D-PAGE separates proteins based on acidity and molecular mass to reveal characteristics of the samples. MS is used for the identification of proteins. NIR spectrometry combined with multivariate analysis can be used for identification of the spectroscopic signature and may be used for further identification of proteins based on fractionation and band assignments. NIR spectroscopy coupled with HPLC, 2D-PAGE, and MS analysis may provide a powerful exploratory tool for the new era of proteomics.

Therefore, NIR spectroscopy coupled with multivariate analysis would provide a powerful tool for exploratory analysis in combination with HPLC, 2D-PAGE, and MS analysis. The accumulated knowledge of the wavelengths at which the different biomolecules absorb using this system will be of great help for targeting the chemical analyses.

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