

# Application of Terahertz Wave Technology in the Biomedical Field

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**Abstract**—This paper introduces a sensing technology that utilizes terahertz (THz) wave with metal mesh resonant filters in the biomedical field. Due to the consistency of energy regions, it is expected to bring about the non-labeling detection of hydrogen bonding and/or intermolecular recognition, as well as antibody responses, etc. Regularly arranged metallic mesh can also be used to make effective use of the THz wave anomalous propagation and absorption characteristics (spoof surface plasmon) of specimens for biopolymer systems, which do not indicate characteristic absorption in the THz band. This paper introduces the THz wave absorption and propagation characteristics in metallic meshes designed for the THz sensing and for application to biomedical related specimens.

**Index Terms**—Terahertz (THz) spectroscopy, biosensors, THz wave surface Plasmon, label-free detection, metal mesh filters.

## I. INTRODUCTION

TERAHERTZ (THz) light has been much needed for a long time, as no stable light source was available. Since the 1990s, however, significant technical developments have occurred. The energy of 1 THz is equivalent to  $33.3 \text{ cm}^{-1}$ , which is equal to 4.13 meV. This vibration mode, with a low energy level, is a characteristic of the THz band (Fig. 1). This energy band of elementary excitation that characterizes substances has a lot to offer. The dielectric soft phonon mode, semiconductor exciton, and bonding modes respond to hydrogen bonding vibrations. These are related to biomolecular systems and intermolecular vibrations, which are associated with the formation of higher order structures of proteins and intermolecular forces of antigen-antibody reactions, which correspond to the THz band energy. It is expected to apply to bio-medical fields [1]–[11], particularly in the application of diagnostics of abnormal tissues. These include cancers [12], [13] and specific proteins, such as amyloids and its relationship to Alzheimer's diseases [14], [15]. It may also be used in the fingerprint spectra of biopolymers, including hydrogen bonding between base molecules. These can be obtained by using THz spectroscopy, particularly with biopolymers, such as DNA [16], [17].

The basic structures of biopolymer materials, such as proteins, are determined by their constituting element types and

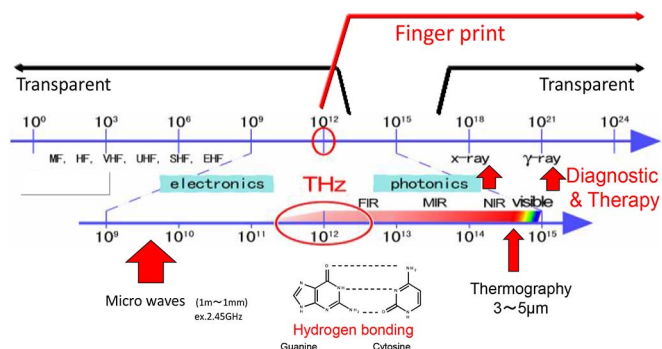


Fig. 1. Relation between frequency and energy value in biomedical applications.

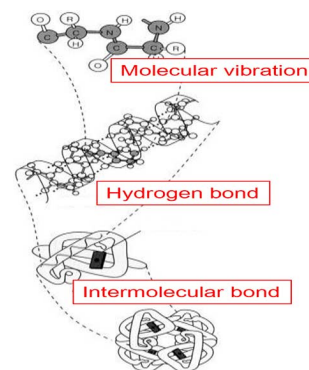


Fig. 2. Higher order structures of bio related molecules.

arrangements (primary structure). The macrophysical properties and functional expressions, such as electrical properties and dynamic properties, however, are determined by uneven structures. These include crystal and amorphous structures, as well as their higher order structures (secondary to quaternary structures) with soft materials, such as proteins, along with bio-related materials (Fig. 2). Proteins, such as amyloid- $\beta$  and  $\alpha$ -synuclein, for instance, are known to trigger both Alzheimer's and Parkinson's disease through changes in their higher order structures [14], [15]. One of the promising advantages of the THz wave is the capability of direct detection for bonding information in a molecular scale (without any chemical modifications). It will enable us to clarify the aforementioned items associated with the formation of higher order structures, as well as hydrogen and intermolecular bonding (London, Kesson and Debye Dispersion Forces). This, along with the unique intermolecular and vibrational energies that form specific bonds which trigger immune reactions such as food allergies and antigen-antibody reactions, are all in the THz wave band.

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TABLE I  
BIO-MEDICAL SENSING TECHNIQUE (CONVENTIONAL AND THz)

Targets	Typical Conventional Techniques	Advantages of Terahertz Technique	Issues to Solve
Bio Chip	Fluorescence (Optical) SQUID (Magnetic)	Label Free Hydrogen bond	Absorption by water Sensitivity
Cell Imaging	Optical microscope Fluorescent microscope Nonlinear microscope	Label Free Non invasion Functional imaging	Absorption by water Spatial resolution
Clinical Diagnosis	XRD, MRI, Ultrasonic Optical CT, Endoscope Biopsy, Fluorescent	Label Free Direct detection of Virus and Bacteria	Absorption by water Spatial resolution
Check on Drug	XRD, Mass Analysis Raman	Crystal Polymorph	Data base

Not requiring fluorescent modifications and the label-free acquisition of the fingerprint spectrum are also advantages of using THz wave technology in relation to bio-related specimens. Little damage is caused to biological specimens, as the energy of the THz light is small. At only a few millielectronvolts (meV), this is also an advantage. Non-destructive and non-contact imaging technologies can be extremely useful for the biomedical field. Once THz imaging and spectroscopic technologies become established that are faster, more sensitive and have higher spatial resolutions, in situ and in vivo vital observations are expected to become possible (Table I).

Though THz wave technology has several beneficial features in biomedical applications, weak and broad THz signal are still issues that must be resolved. Surface plasmon and/or the resonant effect using a metal mesh filter a promising approach for this problem [19]–[27].

## II. THz WAVE PLASMONICS AND TIME DOMAIN SPECTROSCOPY

Ordinary THz time-domain spectroscopy (THz-TDS) involves irradiating extremely short pulses of laser onto a photoconductive antenna. This is done to generate a few ps (up to  $10^{-12}$  s =  $10^{12}$  Hz = 1 THz) of pulses for taking measurements of the pulse waveform in the time domain by using the pump-probe method. This is done after the pulse wave passes through the specimen. The frequency spectrum can be derived by performing the Fourier transformation of the pulse waveform in the time domain. Since information on both the “phase” and the “amplitude” can be simultaneously obtained with this method, it is advantageous in that the real part and the imaginary part of complex dielectric constant can be derived directly by experiment. This is done without going through the Kramers–Kronig transformation. The THz image can also be obtained by scanning the specimen stage in the X- and Y-directions.

The THz wave is expected to be suitable for label-free detections of biopolymers, as they match with the absorption wavelength that arises from intermolecular vibrations between organic and biomolecules, as well as weak hydrogen bonding vibration. There is a problem with the transmission spectrum of gigantic molecules, such as biopolymers that are in the THz band. These assume a broad shape arising from a collective low vibration mode, and do not indicate any characteristic peaks. It is,

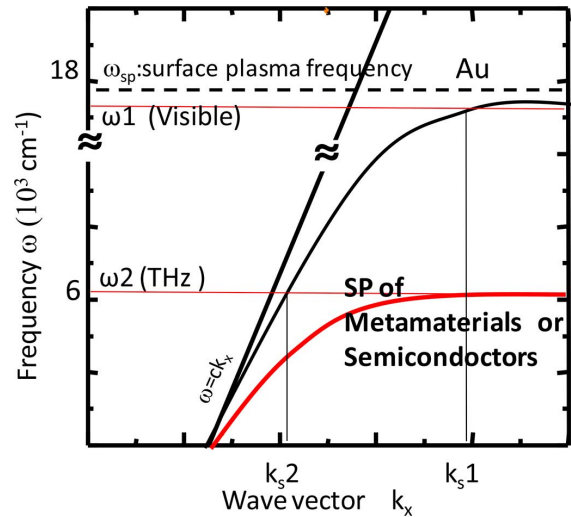


Fig. 3. Surface plasmon of visible and THz wave length.

therefore, difficult to improve on the sensitivity of detection for the purpose of detecting changes in the broad spectrum.

Surface (localized) plasmon phenomenon is a means available to achieve a higher signal to noise ratio and also to enhance the signal intensity. This generally occurs when the real part of the complex dielectric constant arises between a positive (conductor) and negative (metal) material interface. Conditions can be obtained as an intersection of the curve of the wave number ( $k$ )-frequency ( $\omega$ ) and the light line ( $\omega = k/c$ ). Gold and silver/conductors show surface plasmon properties in the visible light wavelength region. But it is difficult to be controlled in the THz region due to poor controllability of the number of carriers. This is done by using semiconductors or nanoscaling. It can also be achieved by using special materials such as graphene (Fig. 3).

There is another effective means of achieving a solution for resolving the issue of measurement sensitive for the broad THz wave spectrum. The THz wave anomalous propagation characteristics of the conducting periodical structure (metamaterial) can be used to create artificial resonance peaks and dips on the THz wave surface plasmon polariton or diffraction evanescent [Fig. 4(b) and (c)] and then observing the changes [Fig. 4(a)] [19]–[23].

Studies have been conducted since the 1960s on metallic mesh with lattice shaped openings. This was used as a band-pass filter for the infrared region and lead to the clarification of frequency characteristics of mesh having various shapes and opening sizes [20], [21]. Improvements with metal processing technologies in recent years has made it possible to manufacture finely detailed periodical structures in a stable manner. These have been used to conduct studies on new optical elements and sensors for the THz band. In 1998, Ebbensen and associates took measurements of transmission spectra of metal films that periodically opened a circular opening with a sub-wavelength diameter in the optical domain. This lead to the discovery and that the measured transmittance was a number of digits higher than those calculated by Bethe on a singular circular opening at specific wavelength [22]. Various studies have been conducted on this phenomenon (anomalous transmission), as they

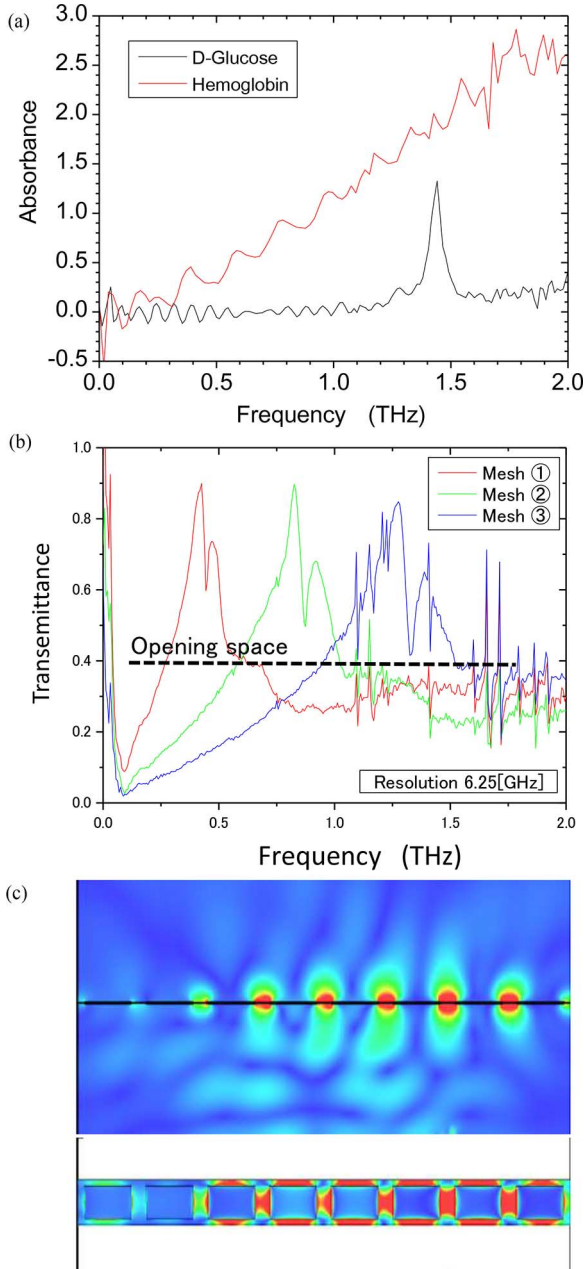


Fig. 4. (a) THz spectra of D-glucose and Hemoglobin. (b) THz spectra of metal mesh (metamaterial). (c) EM pattern by FDTD calculation.

explained that surface plasmon polariton (SPP) was involved in the cause for this [23]–[29]. Thio, Lezec, and associates offered an explanation for the cause of the anomalous transmission with a model using a diffraction evanescent wave in 2004, but details on the mechanism have not yet been clarified [8].

We designed a metallic mesh based on the quantitative empirical formula [22], [23], [30], relating to anomalous transmission characteristics. Fig. 4(b) shows the transmittance spectrum, varying the incidence angle on the metallic mesh. The transmittance far exceeded the area ratio of metallic part and opening part (35%–80%) when the incidence angle was 0 deg. This resulted in the formation of anomalous transmission and dips at more or less the designed frequencies. As the incidence

angle became greater, the dip became deeper and wider. The factor behind the formation of dip has been considered with two models of the surface plasmon and the diffraction evanescent wave [30], [31].

### III. BIOMEDICAL APPLICATIONS

There are three aspects that can be cited as advantages for using THz wave to evaluate bio-related specimens.

The first aspect is the low energy interactions. The energy of electromagnetic waves (light) ( $E$ ) is generally expressed as:

$$E = hc/\lambda$$

Where  $h$ ,  $c$  and  $\lambda$  are Planck's constant, velocity of light and the wavelength of the electromagnetic wave (light), respectively. In comparison with X-ray equipment often used as a means for examinations, the energy required is marginal, at only about one-ten millionth per photon. Since there is no damage to the materials being examined, this can be considered an examination method that is extremely safe and noninvasive for humans that operate the test equipment.

The second aspect is the superior transmittance characteristic. Terahertz wave ( $<3$  THz;  $>\lambda = 100 \mu\text{m}$ ) can pass through high polymer textiles that are universally used for clothing material, without being absorbed. Spectroscopy and imaging using this method can be considered a test technology that is non-contact and non-destructive, which can pass through clothing and applied remotely.

The third aspect is the fact that it offers an appropriately large absorption coefficient in the THz band of 0.5 THz or higher ( $<\lambda = 600 \mu\text{m}$ ) for bio-related specimens and, particularly, for water. On a molecular scale, the hydrogen bonding energy between water molecules exists in the THz band (refer to Fig. 1) [31]–[33]. The THz wave is absorbed by free water that is not restrained by other substances; the property is such that it is not readily absorbed when hydrated in sugar or protein. It is also expected, therefore, to be useful for the quantitative evaluation of various characteristics within vital environments for determining cell states or pharmacological effects. What the THz wave can do for us is not limited to quantitative evaluations of hydrogen bonding that trigger reactions of water solutions or hydration states. It can also provide us with extremely important information on such aspects as the formation of higher order structures and the enzyme reactions of proteins, as well as Van der Waals forces that trigger immune and antibody reactions. A few case examples are introduced below.

#### A. Observation of Hydrogen Bond in DNA Base Pairs

In the bio field, DNA takes on a double helical structure. The absorption of the THz band is known to increase when a single chain becomes a double chain by hybridization. This is believed to be caused by the manifestation of the vibration mode arising from the hydrogen bonding between amino groups of respective bases from complementation of adenine and thymine, as well as guanine and cytosine in THz band. The direct observation of interactions between molecules is possible. Measuring bio-related molecules, including the DNA, can be performed by label-free, non-destructive and non-contact determination of hybridization by using THz spectroscopy [34], [35].



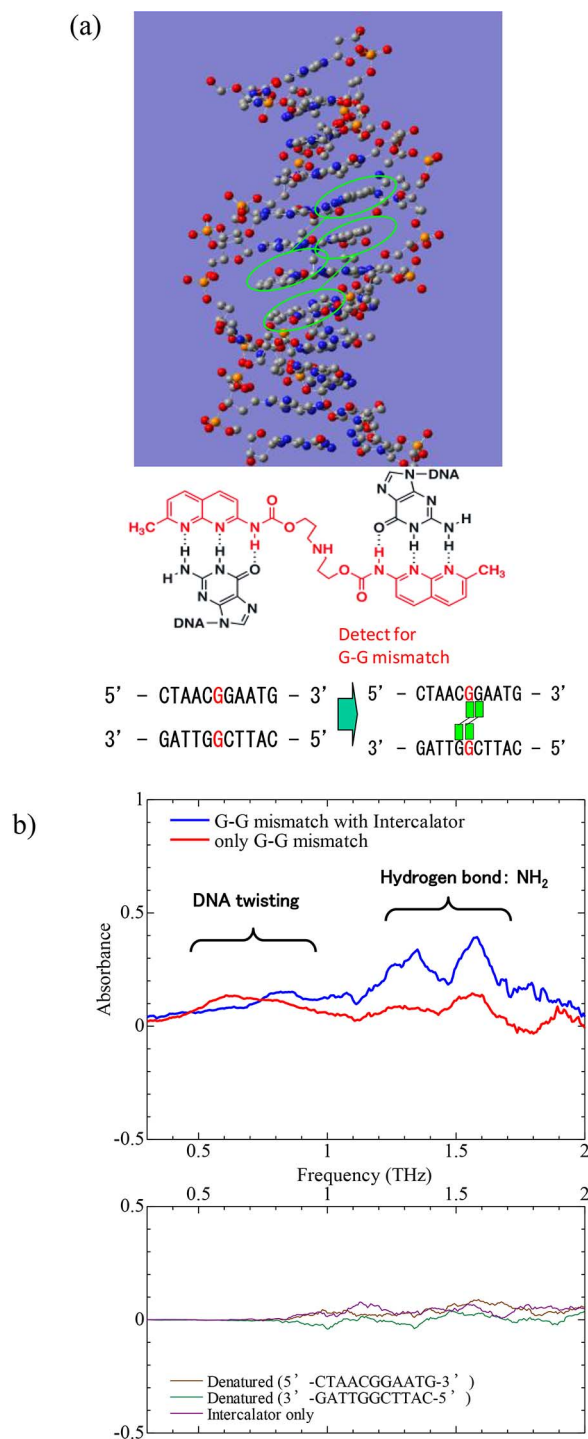


Fig. 5. (a) Artificial DNA for control the number of hydrogen bonds. (b) Terahertz spectra of artificial DNA.

DNA is a representative example of biomolecule, but only broad spectra can be obtained. It is also difficult to gain understanding on such details as attributes of spectrum, since the bonding states of various modes exist. This is because the molecular weight of the DNA is large and as it takes on complex higher order structures. It is, however, still quite useful for accumulating individual experiment data, by targeting artificially controlled base sequence of DNA. That is to say, well-defined

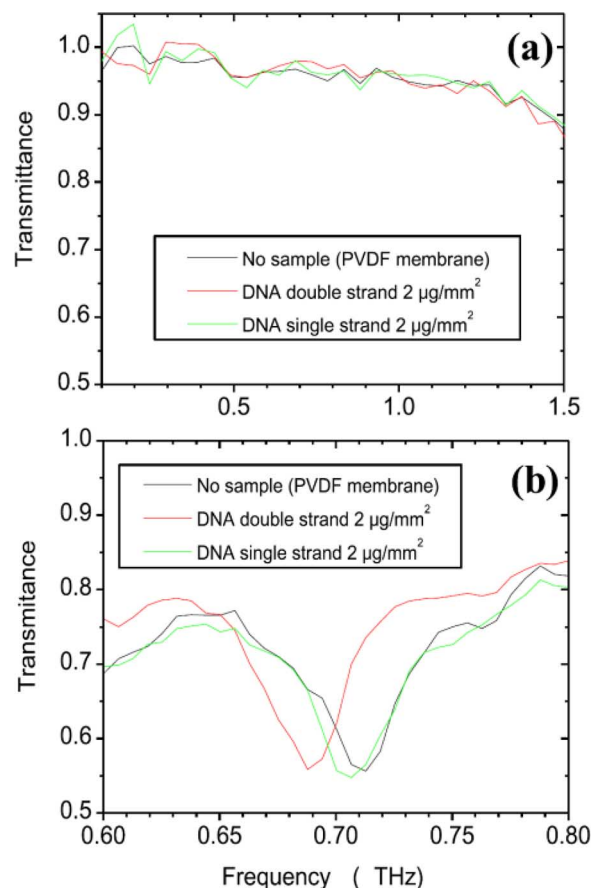


Fig. 6. Terahertz sensing of DNA hybridization: (a) with and (b) without metal mesh.

samples (base sequence and complementary formation controlled for the case of DNA molecules) for measurements and correlating optical spectrum simulations based on theoretical calculations against experiments [36]. We fabricated two types of artificial DNA with the number of hydrogen bonds that were artificially controlled. This was done in collaboration with Professor Nakatani (Osaka University) [Fig. 5(a)]. Absorbance signal around 0.6–0.8 THz and 1.3–1.6 THz correspond to DNA twisting mode and hydrogen bonding mode, respectively. [Fig. 5(b), (c)].

The absorption of peaks in the vicinity of 1.3–1.6 THz were enhanced by insertion of artificially synthesized nucleic base molecules to control the number of hydrogen bonds. This was based on a comparison of the results obtained from a control experiment and a control on the number of hydrogen bonds. This is believed to be caused by the vibration mode that responded to the hydrogen bonding of base pairing (Fig. 6). Reasonable values have been indicated in the vibration analysis for hydrogen bonding, between the base molecules derived by simple semi-empirical molecular orbital calculation, as well [36], [37].

#### B. Label-Free (Non-Fluorescent Modified) High Sensitivity Detection of Sugar-Lectin Specific Bonding

Sugar chain is the third important biopolymer system, after nucleic acid and protein. It is an index for diagnosing bioactivity and diseases, allergies, and virus infections. When such

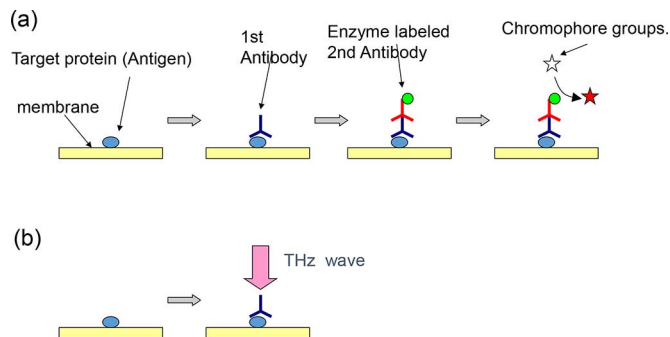


Fig. 7. Detection of specific binding: (a) with and (b) without labeling.

a sugar chain is specifically recognized, and if the protein that bonds and bridges is lectin, there is a close relevance with immune activity, food allergy, food poisoning, food hypersensitivity and lectin intolerance. In addition to the primary antibody, the chemical modification of the secondary antibody and fluorescent molecules is necessary with conventional food allergy testing conducted by the ELISA method. This is because fluorescent molecules (labeling) are required, as shown in Fig. 7. The direct measurement of the bonding of antigenic substances (molecules) on antibodies is possible when utilizing the characteristics of the THz wave, as described in the previous chapter [38]–[41].

Concanavalin A (ConA) was used for lectin, glucose (Glc), Mannose (Man), N-acetylglucosamine (GlcNAc) and galactose (Gal) were used for sugar in the label-free THz wave detection experiment for the lectin-sugar chain interaction. The spoof surface plasmon phenomenon, using metamaterials, was used to improve sensitivity.

First, the PVDF membrane was immersed in alllection solution for one hour. It was then immersed in the 2.5% glutaric aldehyde solution for 10 min, to immobilize lectin. Ultra-pure water was used to rise for three sessions of five minutes. The membrane was then immersed in sugar solution for one hour. After, the membrane was washed with ultra-pure water for 5 min and dried. A metal mesh (period of 302  $\mu\text{m}$  and metal width of 74  $\mu\text{m}$ ) was then bonded to the membrane and a measurement was taken using the THz time-domain spectroscopy, with an incidence angle of 7 deg. The following were used as measurement samples.

- 1) *Quantitative measurements*: The concentration of lectin (ConA) was maintained at 50  $\mu\text{M}$ , while the concentration of sugar (Glc) was varied to 0, 5, 10 and 50 mM.
- 2) *Qualitative measurements*: The concentration of lectin (ConA) was maintained at 20  $\mu\text{M}$ , while the type of sugar (Glc, Man, GlcNAc and Gal) was varied with 10 mM concentration.

First, attention was focused on the dip of the THz wave absorption spectrum. Both the amount of shift in dip frequency and the attenuation of the transmittance for the dip frequency were measured. It is evident that increasing the concentration of Glc shifted the dip frequency with the transmittance spectrum towards the lower frequency side, while increasing the attenuation of transmittance for the dip frequency. This is believed to be due to the fact that, as the bonding amount of lectin (ConA) and sugar (Glc) becomes greater, the refractive index (dielectric

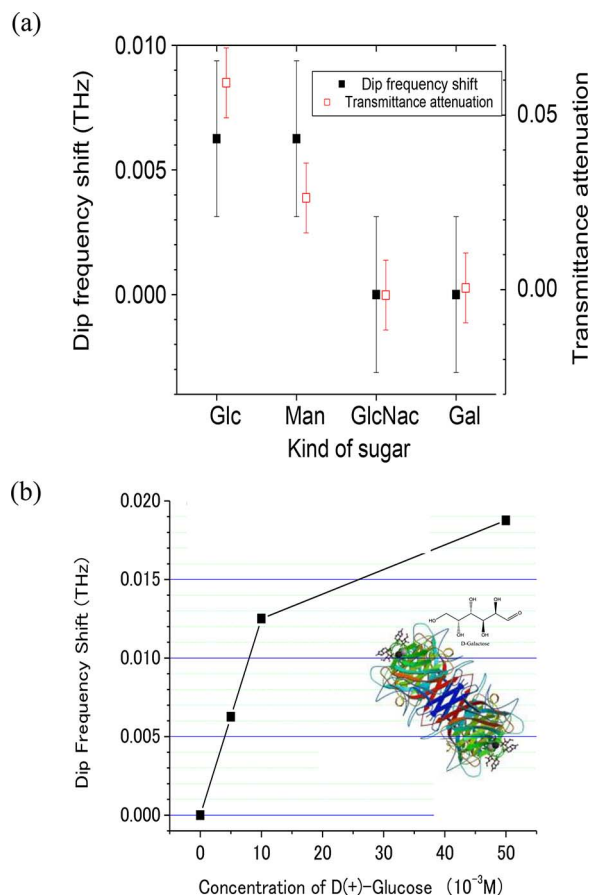


Fig. 8. Non labeling detection of sugar-lectin interaction Detection of antibody-antigen binding by THz spectra. (a) Variation of several lectins and (b) dip frequency shift versus concentration of glucose.

constant) of the PVDF membrane becomes greater. The bonding constant was calculated from experiment values to be  $100\text{ M}^{-1}$ , which was a value that was close in terms of digits to the [18] of  $600\text{ M}^{-1}$  that had been reported in the past.

Attention was focused on the dip of the transmittance spectrum in a similar manner. The representation of the shift in dip frequency and the attenuation of the transmittance for the dip frequency are shown in Fig. 8. In the reaction of Glc and Man, it is evident that the dip frequency had shifted toward the lower frequency side and the attenuation of transmittance for the dip frequency had become larger. It is evident that no shift in the dip frequency was observed with the reaction of GlcNAc and Gal, where the attenuation of transmittance for the dip frequency was also small. There is specificity with lectin for a bonding reaction with sugar. ConA is known to indicate specific bonding with Glc and Man, while no specific bonding is indicated with GlcNAc and Gal. Since performing a washing treatment after the reaction between lectin and sugar washes away practically all of GlcNAc and Gal, the change in the refractive index of the PVDF membrane is small. The refractive index of the PVDF membrane is believed to become greater, since the bonded portion of Glc and Man with lectin (ConA) remains even after washing treatment.

It became evident that the bonding evaluation of sugar with lectin could be performed with no chemical modifications by using the THz wave technology, as described above. More

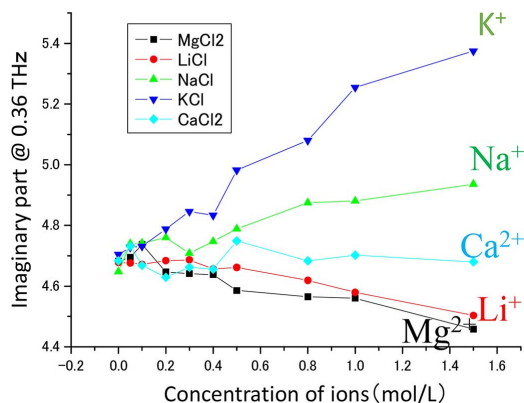


Fig. 9. Concentration dependence of imaginary part of reflectance of various cations of  $K^+$ ,  $Na^+$ ,  $Li^+$ ,  $Mg^{2+}$  and  $Ca^{2+}$  measured by THz.

specifically, the evaluation was successfully completed by identifying the specific bonding for the types of sugar (glucose and mannose) and nonspecific adsorption (N-acetylglucosamine and galactose) from dip shifting in the label-free THz detection of specific bonding between lectin (ConA) and sugar (glucose, mannose, N-acetylglucosamine and galactose). The distinction between the specific bonding and nonspecific adsorption is believed to be possible, as the energy domain of the THz wave is equivalent to the intermolecular vibrations of biomolecules and hydrogen bonding vibrations [42].

### C. Hydration State Evaluation of Bio-Related Ions

The absorption coefficient of the THz wave is substantial ( $200 \text{ cm}^{-1}$ ) in free water (free water molecule in solution), as described above. On the other hand, its property makes it difficult to be absorbed by bound water (water molecules forming hydration state with dissolved substances) [32]. The existence of water, is extremely important in the bio field. The bio-essential ions and folding phenomenon of proteins act as energy source to trigger vibration of molecules in the vicinity of proteins. The determination of higher order structures is influenced by the protein structures of the hydrophilic group and the hydrophobic group [33]. Transmittance measurement was performed on the variation of hydration quantity in relation to the univalent ions of Li, Na and K, as well as the divalent ions of Mg and Ca using THz wave spectroscopy; this was done in order to gain better understanding of this property. Such ions of elements formed a hydration state with surrounding water. This resulted in the reduction of free water and an increase of bound water, leading to the expectation that a change in the transmittance of THz wave to occur. Fig. 9 depicts the calculation for the hydration state of various ions that exist within 300 molecules of water, using a large-scale molecular dynamics calculation.

Water molecules have a large bipolar moment of 1.83 D (debye), as described in Section I, with a property of hydrogen bonding with polar groups as proton acceptors or donors. The interaction with water, which is a solvent for ions and molecules, is referred to as hydration. The solvation state is closely related to the surrounding ions, size of molecules, valence and number of bonding sizes (Fig. 10).

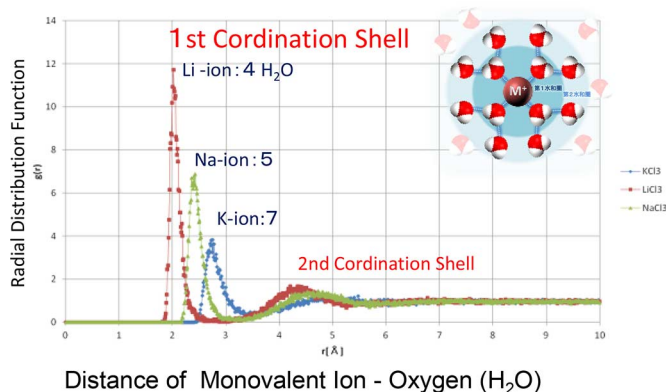


Fig. 10. Hydration state of mono-valent cations by MD calculation.

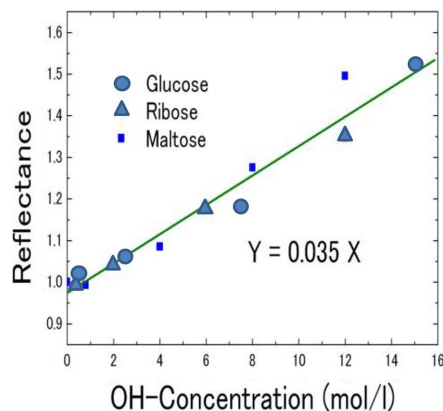


Fig. 11. Reflectance at 0, 5 THz of sugar groups against number of OH-concentration.

Measurements of multiple sugar types were taken to evaluate the hydration amount due to hydroxyl group. Monosaccharides (glucose), pentose (ribose) and disaccharides (maltose) were used as samples. It is a widely known fact that the OH group forms hydrogen bonds with water molecules. For this purpose, let us consider the experiment results, beginning with the number of OH groups included in each type of sugar. The number of OH groups contained in a single molecule of each sugar type is five for glucose, four for ribose and eight for maltose. No significant change in the reflection coefficients is observed up to 0.5 mol/l in the experiment results for the three types. The reflection coefficients for the three types varied in the results, starting from 1.5 mol/l onwards. There is hydrogen bonding in sugar molecules and the number of hydrations per molecule of solute with low concentration is determined relatively without any relevance to the number of OH groups. Sorting out the amount of hydration per molecule of solute beyond a certain concentration, with respect to the number of OH groups that comprise molecules of solute and the concentration of the number of specific sites (OH groups), as well as THz wave reflection coefficient, indicates a proportionality relation as shown in Fig. 11. This means that it becomes possible to predict the number of functional groups that form hydrogen bonding with water molecules that form solvation of targeted substances from the THz wave measurement. This makes it possible to obtain information that is important for evaluating hydration states [43].

#### IV. SUMMARY AND FUTURE OUTLOOK

The incidence angle of the THz wave on metal mesh designed for anomalous transmission and dip frequencies at the intended positions, was varied to indicate that the dip frequency linearly shifted towards the lower frequency side. While it is possible to perform an overview using the surface plasmon polariton and equation of diffraction evanescent wave proposed in the past, it is necessary to implement terms relating to opening surface for more rigorous examinations. It became evident that a completely new dip occurred with an inclination beyond a certain degree. It also became clear that detection with sensitivity of about 50 times that of the avidin-biotin reaction detection was possible using the HABA method. This is generally available as an immunity measurement method. The detection of the biotin amount, at the level of  $0.1 \text{ pg/mm}^2$ , was possible with THz light absorption measurement (label-free measurement), using such geometrically specific peaks. An advantage of THz spectroscopy for bio-related specimens is that a fingerprint spectrum can be obtained without any need for fluorescent modifications and no labeling. Another advantage is the small energy of THz light. At only a few meV, it causes little damage to biological specimens. The fact that non-destructive measurements can be performed on precious specimens, such as geological or archaeological specimens, is also an advantage. Once THz imaging and spectroscopic technologies are faster, more sensitive and have higher spatial resolutions established in the future, in situ and in vivo vital observations will most likely become possible.

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