Nanoantenna Enhanced Terahertz Interaction of Biomolecules

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Terahertz time-domain spectroscopy (THz-TDS) is a non-invasive, non-contact and label-free technique for biological and chemical sensing as THz-spectra is less energetic and lies in the characteristic vibration frequency regime of proteins and DNA molecules. However, THz-TDS is less sensitive for detection of micro-organisms of size equal to or less than $\lambda/100$ (where, $\lambda$ is wavelength of incident THz wave) and, molecules in extremely low concentrated solutions (like, a few femtomolar). After successful high-throughput fabrication of nanostructures, nanoantennas and metamaterials were found to be indispensable in enhancing the sensitivity of conventional THz-TDS. These nanostructures lead to strong THz field enhancement which when in resonance with absorption spectrum of absorptive molecules, causing significant changes in the magnitude of the transmission spectrum, therefore, enhancing the sensitivity and allowing detection of molecules and biomaterials in extremely low concentrated solutions. Hereby, we review the recent developments in ultra-sensitive and selective nanogap biosensors. We have also provided an in-depth review of various high-throughput nanofabrication techniques. We also discussed the physics behind the field enhancements in sub-skin depth as well as sub-nanometer sized nanogaps. We introduce finite-difference time-domain (FDTD) and molecular dynamics (MD) simulations tools to study THz biomolecular interactions. Finally, we provide a comprehensive account of nanoantenna enhanced sensing of viruses (like, H1N1) and biomolecules such as artificial sweeteners which are addictive and carcinogenic.

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I. INTRODUCTION

Optical antennas,\textsuperscript{1,2} devices converting free optical radiations into localized ones, and vice versa are important components in modern nanophotonic devices. In the recent decade, metallic nanoantenna has attracted much consideration with the significant advancement of nanofabrication technologies, which provide the feasibility of fabrication at nanometre resolution, enabling fascinating nano-optoelectronic devices. Since metals exhibit finite conductivities and plasmonic effect at optical frequencies, therefore the optical field response is dictated by the resonance oscillation of electron clouds (surface plasmons, or SP) in the metal, coupling with the incident photon and sustaining surface plasmon polaritons (SSPs).\textsuperscript{3,4} Henceforth, at optical frequencies a nanoantenna, depending upon the material properties, resonates for considerably shorter effective wavelength, rather than half-wavelength of free-space.\textsuperscript{5,6}

Electromagnetic interaction of nanoantennas has lead to huge local field enhancement and confinement in nano-size volumes, enabling broadband application in nano-optics.\textsuperscript{7–15} Terahertz (THz) wave funnelling through nanogaps/nanoantennas has resulted huge field enhancement.\textsuperscript{16–40} Figure 1 summarizes the various investigations performed to study the THz field enhancement with different gap sizes. Such investigations have lead to the development of the terahertz technology, which are now exploited in electronics,\textsuperscript{41–46} photonics,\textsuperscript{47–49} medical sciences,\textsuperscript{50–52} military,\textsuperscript{53–55} security\textsuperscript{56,57} and conservation of cultural heritages.\textsuperscript{58,59} These studies also lead to the improvisation of terahertz devices.\textsuperscript{60–76}
is a non-invasive and one of the most widely used technique in biosensing because the THz-spectra are less energetic (about a few milli-electronvolts) lies in the characteristic vibration frequency regime of proteins and DNA molecules. Terahertz nanoantennas provide us label-free and ultra-sensitive sensing of molecules and biomolecules as the nanoantennas focus the THz waves into an extremely confined volume where we can place our analytes at very low concentrations. Significant changes in the magnitude of the transmission spectrum were observed in the absorptive molecules when the resonance mode of the waveguide matches its absorption spectrum, enhancing the sensitivity of THz-resonators based sensing devices, therefore making it feasible for detection of biomolecules at extremely low concentration.

In this review work, we describe the high-throughput fabrication techniques of THz nanoantenna via photolithography, atomic layer lithography, pattern and peel method, self-assembly lithography etc. Then we discuss the THz field enhancement using metal nanogap antenna where we discuss the field enhancement beyond the skin depth of the metal up to the quantum regime. Then we briefly discuss finite-difference time-domain (FDTD) methods for calculation of field enhancement across the nanogap. At the last, we describe the THz-TDS for sensing the biomolecules due to the field enhancement across the nanogap. We also showed how a molecular dynamics (MD) simulation can be a versatile tool to estimate the terahertz absorption and vibrational density of states (VDOS). Then we have taken real examples from various literature that how THz nanoantenna and metamaterials can be used to enhance the terahertz biomolecular sensing.

II. HIGH-THROUGHPUT WAFER-SCALE FABRICATION TECHNIQUES

A nanogap must have a reliable THz-field interaction and plasmonic characteristics (like, field enhancement
and non-linearity). But fabricating high throughput wafer-scale nanogaps is one of the most challenging parts of the job. To achieve sufficiently intense far-field signals, nanogap arrays should be fabricated over large sample area. Several methods like: fs-laser beam machining,\textsuperscript{17,96–98} focussed ion beam,\textsuperscript{17,40,99–104} photolithography,\textsuperscript{17,105–108} electron-beam (e-beam) lithography,\textsuperscript{17,109–115} nanosphere lithography,\textsuperscript{17,116} sidewall lithography,\textsuperscript{117} nanoimprint,\textsuperscript{17,118–122} pattern and peel method,\textsuperscript{123} and atomic layer lithography\textsuperscript{17,41,95,124–126} have been developed for high resolution patterning over large area of sample.

Photolithography,\textsuperscript{17,23} (Fig. 2) is one of the most high-throughput methods for fabricating nanogap structures. In photolithography, a desired polymer pattern is patterned using ultraviolet (UV) light and a photomask. This polymer pattern is formed by the physical change of a photo-sensitive material, known as photoresist (PR).

Polymers added to PR decides the solubility under UV exposure. A PR which consist of an insoluble polymer which on UV exposure, changes into a soluble polymer, is called a positive PR and a PR which consist of a soluble polymer which on UV exposure, polymerizes and becomes insoluble, is called a negative PR. Therefore by using the desired PR, wafer-scale metal structures are fabricated after performing a metal deposition process on patterned resists and lift-off of the unwanted metal film.

The lithography method discussed earlier are limited to fabrication of nanometer-gaps up to a few nanometers. To study the nano- and sub-nanoscale optics, we need better lithography techniques to fabricate sub-10 nm wide gap. Many researchers have reported the significance of deposition of an atomically thin insulating layer or sacrificial layer in fabricating small gaps between two metal structures.\textsuperscript{127–132} Chen et al.\textsuperscript{95} developed a pioneering method for fabricat-
Ion Milling  
Coating  
Al/Cr Wet Etching  
Al2O3 Coating  
Cr/Au Deposition  
Cr/Au Film  
Cr/Al Pattern  
Ion Milling

Figure 4. High-throughput fabrication technique of nanometer-scale gaps introduced by Jeyong et al. Adapted with permission from Ref.22. © 2014, Springer Nature.

ioning vertical nanogaps known as atomic layer lithography (Fig. 3 (A - D)). Figures 3 (E - G) are the scanning electron micrographs (SEM) of 5 nm gap in Ag film, 10 nm gap between Au and Ag, and 9.9 Å Au - Al₂O₃ - Au vertical nanogap, respectively, which are fabricated using atomic layer lithography technique. This method also includes a new planarization scheme which eliminates the background light transmission, enabling background-free transmission measurements. This lithography technique is the combination of atomic layer deposition (ALD) and ‘plug-and-peel’ adhesive tape planarization and is a three-step process. The first step includes the pre-patterning of metal using conventional lithography techniques, the second step includes the sidewall formation of materials like Al₂O₃ or SiO₂ by ALD, and the third step includes the ‘plug-and-peel’ taping process for planarization of metal plugs. Therefore, atomic layer lithography is a high-resolution patterning method with large scale uniformity.

Jeyong et al.22 improvised the atomic layer lithography technique which is demonstrated in Fig. 4. In this lithography technique, conventional photolithography and liftoff process were used to pattern 30 nm Cr/150 nm Al layer on the 3 nm Cr/100 nm gold-sapphire substrate. The Cr-Al double layer acts as a sacrificial layer which will be etched out later, removing excess metal and making the structure planar. As compared to Al, Au is less-resistant to ion beam therefore, excluding the Au film beneath Al-Cr layer, the exposed Au layer is removed using ion milling process. Uniform ALD of Al₂O₃ is performed over the whole structure with a thickness of nanometer accuracy. After that, the second layer of Au with adhesive Cr is deposited, filling the trenches. Finally, Al/Cr wet etching is performed which removes the overhanging Au and Al layers, exposing the dielectric gaps. This lithography technique can be used to fabricate large-scale nanogaps with ultra-high aspect ratio.

Tripathi et al.133 developed self-assembled lithography process by which they fabricated quantum dots (QDs) nanogap metamaterials (Fig. 5). In this lithography process, photolithography was used to pattern PR on a clean and dried sapphire substrate. With the help of a thermal evaporator (evaporation rate = 1 Å/sec), a chrome layer of thickness 10 nm was deposited over the PR pattern. Following the process, a silver film of thickness 200 nm was evaporated over the chrome layer. After the evaporation of first silver layer, the whole sample was then dipped in acetone sonicated for 2-minutes at 150 W and 36 kHz, lifting off the PR pattern. After sonication, the sample was washed with isopropyl alcohol and dried using N₂ gas. The dried sample was then dipped into a toluene solution of OT (1-8 octanedithiol) functionalized QDs, resulting in the formation of a self-assembled monolayer of QDs. The resulting sample was again dried using N₂ gas and a second silver layer of same/higher thickness was deposited over the self-assembled monolayer. Then by using aesc tape,95, the second layer of silver was taped-off, leaving a vertical metal nanogap filled with a monolayer of QDs.

III. TERAHERTZ-FIELD ENHANCEMENT USING NANOANTENNAS

In THz frequency, a metal film is not a perfect conductor as well as infinitely flat. Equivalence of THz-electric field enhancement in metal nanogap18,28,34,35,134-136 and magnetic field enhancement around metallic nanoantennas137-140 can be shown by using Babinet’s principle.141-145 This principle is still used implicitly in different areas of THz research.22,27,36,38,42,93,103,107,146-168 Sommerfeld’s half-plane problem169-171 is also used to study the light-aperture interaction theoretically. Bette172 and Bouwkamp173,174 reconsidered the Sommerfeld’s half-plane problem for small apertures in infinitely thin perfect conducting plates. Further studies were performed on the light interaction with system of periodic apertures.175 Later, extensive studies were performed on enhanced light transmission through the apertures in various spectral regime.19,31,32,102,176-180 Theoretical approaches like: coupling-mode theory,135,181-188 microscopic models,28,29,189 transfer-matrix method190,191 and capacitor model134 were combined with numerical methods76,192,193 to solve the enhanced light transmission and huge field enhancement around metallic apertures.

When an electromagnetic wave is incident normally on a perfectly conducting metallic plane, an induced current is developed on the surface, which reflects light back, with no charge accumulation anywhere.34 When this plane is divided into two perfectly conducting Sommerfeld half planes, macroscopic accumulation of charges take place at the edges with a length scale of one wavelength, such that the surface charge density (σ) depends as a time function for small values of x ≪ λ,34
Figure 5. Self-assembly lithography technique. (A) Clean and dried sapphire substrate. (B) PR patterned using photolithography. (C) 10 nm chrome layer deposition over PR pattern. (D) Evaporation of silver film of thickness 200 nm over the chrome layer. (E) Sonication and lift-off of PR after first silver layer deposition. (F) Self-assembly of QD monolayer over the first layer of metal. (G) Second silver layer deposition after self-assembly of QD monolayer. (H) QDs filled nanogap metamaterial after taping-off second silver layer. Adapted with permission from Ref. 133. © 2015, Optical Society of America.

given by

\[ \sigma(x, t) = \frac{\epsilon_0}{\sqrt{2\pi}} \sqrt{\frac{\lambda}{x}} E_0 e^{-i(\omega t + \pi/4)} \]  

(1)

Here, \( \epsilon_0, E_0, \omega \) and \( x \) describes the permittivity of vacuum, the incident electric field, the angular frequency and distance from the edge, respectively.\(^{144} \) The charge singularity, at \( x = 0 \), for this half plane is very feeble and disappears with integration. When the two metallic half planes are brought close together, an electrostatic force will be experienced by the charges due to their counter members across the gap, pulling the charges towards the edge, and developing a strong electric field across the gap. As the gap shrinks, more charges gets accumulated at the edges as the light-induced currents becomes more and more stronger. This increases the surface charge density at the edges as shown in Fig. 6 B - C. This system can be portrayed as a line-capacitor driven by the light-induced alternating current as shown in Fig. 6 (A).

Numerous studies have reported the monotonic enhancement of the electric field with decreasing gap size.\(^{34,93,95,145} \) Further studies have also reported the decrease in field enhancement when the gap size decreases and enters a quantum regime.\(^{24,194–199} \) Increase in field enhancement beyond sub-skin depth is also reported.\(^{16,23,34} \) In this section of the review, we discuss the THz field enhancement for gaps beyond skin-depth and also in the quantum regime. We also discuss the classical limit of field enhancement of single nanoslit before entering quantum regime, and about finite-difference time-domain algorithm, which is a computational approach developed for the quantiative estimation of far- and near-field enhancement measurements.

### A. THz Field Enhancement in Metal Nanogaps at Sub Skin-Depth Regime

In this part of the section, we discuss the skin-depth physics\(^{23} \) and the results reported in various literatures\(^{16,34} \). Consider two perfectly conducting metallic planes of thickness \( h^{16,134} \) kept at a distance \( w \) from each other, forming a metal-air-metal nanogap. An electromagnetic wave is incident normally on the metal nanogap whose electric field has a magnitude of \( E_0 \). Then the ultimate field enhancement in a high-aspect ratio \( (w/h \gg 1) \) is given by\(^{23} \)

\[ E_{\text{enhancement}} = \left| \frac{E}{E_0} \right| = \frac{\lambda}{\pi h} \]  

(2)

where, \( E \) denotes the electric field at the gap and \( \lambda \) denotes the wavelength of the incident electromagnetic wave in vacuum. If a dielectric material of permittivity
The thickness at which the absorption loss by metal is 50%, is known as the characteristic thickness ($h_0$). For a metal with conductivity $10^\text{7} \\Omega^{-1} \text{m}^{-1}$, the characteristic thickness is 0.53 nm. At 1 THz, the skin-depth is about 100 nm or more for good metals. Therefore, the thickness range for transitional metal film is 5-100 nm. The electric field amplitude transmission ($t$) and reflection coefficient ($r$) for such thin films are given by

$$t = \left| \frac{E_t}{E_0} \right| \approx \frac{2\varepsilon_0c}{\sigma_m h} = \frac{h_0}{h} \ll 1; \quad r \approx 1 - \frac{h_0}{h} \approx 1$$

where, $E_t$ denotes the transmitted electric field.

Considering a transverse magnetic polarized light ($E_x$, $H_y$) is incident normally on a thin metal film. Due to reflection from the incident surface, the magnetic field of the light near the incident surface becomes twice that of the incident magnetic field. But the magnetic field on the transmission side is much smaller than the incident field (Fig. 7 (B)). Assuming that a constant electric field/current density is developed inside the thin film, using Ampere’s law, the expression of the current density inside the thin film is $J = \frac{2\varepsilon_0c}{\sigma_m h} h_0$ (neglecting vacuum displacement current).

Here, $J$ denotes the current density developed inside the thin metal film and $H_0$ denotes the incident magnetic field. The tangential component of electric fields at the air-metal interface are continuous and is given by

$$E_l = E_m = \frac{J}{\sigma_m} = \frac{2\varepsilon_0c}{\sigma_m h} = \frac{2\varepsilon_0c}{\sigma_m h} E_0$$

therefore, reproducing Eq. 4. At transmitting side, electric field just inside the metal surface is denoted as $E_m$.
Across the air nanogap, the normal component of the displacement current will be same (Fig. 7 (C)), therefore electric field inside the air nanogap will be

\[ E = \frac{e_m}{e_0} |E_m| \approx \frac{\sigma_m}{\varepsilon_0 \omega} \frac{2e_0 c}{\varepsilon_0 \omega \sigma_m h} E_0 = \frac{\lambda}{\pi h} E_0 \]  

(6)

where, \( e_m \) denotes the terahertz metal dielectric constant given by

\[ e_m = e_\infty + i \frac{\sigma_m}{\omega} \left( \frac{1}{1 - i\frac{\omega}{\gamma}} \right) \approx i \frac{\varepsilon_m}{\omega} \]  

(7)

where, \( e_\infty \) denotes the dielectric constant of metal at high-frequency and \( \gamma \) denotes the Drude damping constant.

**B. THz Field Enhancement in Sub-Nanometer and Ångstrom Metallic gaps: Quantum Regime**

Recently, Bahk et al.\(^{16}\) discussed about the field enhancement in thin (\( w \sim h < \delta \)) and thick (\( w < \delta < h \))
narrow gaps, and in wide ($\delta, h < w$) gaps. In wide gaps, the charges are mostly spread over the surface outside the gap rather than at metal edges (Fig. 6 (B)), which results in a decrease of field enhancement. In narrow gaps, charges mostly accumulate at the metal edges of the gap (Fig. 6 (C)), resulting in stronger field enhancement. As the width of the gap ($w$) decreases further entering the sub-nanometer and Ångstrom regime, the charge distribution becomes insensitive to gap size and electron tunnels through the potential barrier of the nanogap, showing quantum effects.\textsuperscript{197,199–210} When THz electromagnetic waves are incident on the nanogap, a transient voltage is developed in the dielectric gap which bends the conduction band of the dielectric toward the Fermi energy of metals (Fig. 9).\textsuperscript{24} This increases the chances for electron tunneling through the potential barrier, causing non-linear transmissions.

Bahk et al. also investigated the classical limit of field enhancement before the gap-width entered the quantum regime.\textsuperscript{16} They reported that the field enhancement exhibited saturation behavior rather than a monotonous increasing nature. This showed that the nanogap acts like a charged capacitor\textsuperscript{34} which is shown in the Fig. 6 (A), whose total induced charge is inversely proportional to the frequency of a light-induced alternating current of THz-frequency. FDTD analysis of the electric field distribution around 1.5 nm wide gap in 150 nm thick gold film at a frequency of 1.5 THz, as shown in Fig. 10 (A). As expected the horizontal electric field is strongly concentrated and is enhanced by a factor of 2000 inside the gap. Fig. 10 (B) shows the electric field enhancement in different gap size for various frequencies. The theoretical calculation of the modal expansion for the perfect electric conductor (PEC) model is shown by solid lines.

C. The Finite-Difference Time-Domain (FDTD) Algorithm: A Computational Electromagnetism Approach

The finite difference time domain (FDTD) method\textsuperscript{211} is used to solve Maxwell’s equations in the time domain and generally used for computational electrodynamics.

\[
\nabla \cdot \vec{D} = \rho \quad (8)
\]

\[
\nabla \cdot \vec{B} = 0 \quad (9)
\]

\[
\nabla \times \vec{E} = -\frac{\partial \vec{B}}{\partial t} \quad (10)
\]

\[
\nabla \times \vec{H} = \vec{J} + \frac{\partial \vec{D}}{\partial t} \quad (11)
\]

are the four Maxwell’s equations where, the electric field, magnetic field, electric displacement field, magnetic flux density, free electric charge density, and free current density are denoted by $E$, $H$, $D$, $B$, $\rho$ and $J$, respectively.\textsuperscript{212,213} These equations are solved numerically on a discrete grid in both space and time, and derivatives are handled with finite differences. No approximations or assumptions are made about the system, making this method highly versatile and accurate. It is a fully vectorial simulation method as it solves for all electric and magnetic field vector components. Being a time-domain method, FDTD can be used to calculate broadband results from a single simulation. FDTD method is typically used when the feature size is of the order of the wavelength. It is general, versatile, accurate, broadband and fasts which makes it the most reliable method in computational electrodynamics.

FDTD algorithm solves Maxwell’s curl equations in non-magnetic materials.

\[
\frac{\partial \vec{D}}{\partial t} = \nabla \times \vec{H} \quad (12)
\]

where, $\vec{D} = e \vec{E}$. Since the region is vacuum, $\vec{J} = 0$.

\[
\vec{D}(\omega) = e_0 e_r(\omega) \vec{E}(\omega) \quad (13)
\]
\[ \frac{\partial \vec{E}}{\partial t} = -\frac{1}{\mu_0} \nabla \times \vec{H} \quad (14) \]

with H, E, and D describing the magnetic field, electric field and displacement field, respectively, while \( \varepsilon_0(\omega) \) is a complex relative dielectric constant given by

\[ \varepsilon_r(\omega) = n^2 \quad (15) \]

\( n \) denotes refractive index of the material. In 3-D, the six electromagnetic components of Maxwell’s equations are \( E_x, E_y, E_z \) and \( H_x, H_y, H_z \). Assuming that in z-dimension, the structure is infinite and the fields are independent of z, such that \( \varepsilon_r(\omega, x, y, z) = \varepsilon_r(\omega, x, y) \), and

\[ \frac{\partial \vec{E}}{\partial z} = \frac{\partial \vec{H}}{\partial z} = 0 \quad (17) \]

then, two independent sets of Maxwell’s equations will be created. Each set will contain three vector quantities which can only be solved in x-y plane. The equation containing the components \( E_x, E_y, E_z \) is known as transverse electric (TE) equation, and the equation containing the components \( H_x, H_y, E_z \) is known as transverse magnetic (TM) equation.

\[ \frac{\partial D_z}{\partial t} = \frac{\partial H_y}{\partial y} - \frac{\partial H_x}{\partial x} \quad (25) \]

\[ \frac{\partial D_y}{\partial t} = \frac{\partial H_z}{\partial z} \quad (26) \]

These equations are solved on a discrete, spatial and temporal grid. Each field component is solved at a slightly different location within the grid cell (or, Yee cell).\(^{211}\)

With this method we can simulate the electric and magnetic fields around any nanostructures using commercially available softwares like, FDTD Solutions (Lumerical Inc., Canada), COMSOL, etc. Fig. 11 shows the FDTD analysis of gold nanogap (100 nm thick and wide gap) and nanorod, respectively.\(^{145}\)

**IV. THZ-TDS AND SENSING OF MOLECULES AND BIOMOLECULES**

In the late 1980s, Grischkowsky et al.\(^{214-216}\) introduced the terahertz time-domain spectroscopy technique (Fig. 13). It is a spectroscopic technique in which short-THz pulses are used to probe the properties of matter. The system generally consisted of the femtosecond laser (fs-laser), which operates at a repetition rate of 100 MHz, producing a 100 fs laser pulse train. Using a beam splitter, the fs-pulse train is split into two...
A. Computational THz-TDS using Molecular Dynamics (MD) Simulation

MD simulation is a computational method used to study the dynamics of a system of molecules in the condensed phase. To accurately study the dynamics of a complex molecule, one needs to employ the quantum model to study the wave function of each sub-atomic particle. But MD employs classical Newtonian mechanics to study the dynamics of the system, which makes it less accurate. Specifically, it integrates Newton’s equation of motion in discrete time-steps. Due to high THz absorption by water, THz-TDS becomes challenging for water-based systems. Therefore, MD simulation is one of the preferred methods to study the water dynamics of a hydrated molecular system. In MD, water dynamics has a great significance in the structural arrangements of molecules, which occurs because the molecule alters the dynamics of the surrounding water molecules, adopting a quasi-coherent character, caused by reorganized, loose beams: a pump beam and a probe beam. The pump beam is made to be incident on a THz emitter to emit THz pulses, which is collimated to the sample using a pair of parabolic mirrors. Concurrently, the probe beam is used in a time-gated manner for the detection of THz electric field which contains time-domain information of phase and amplitude. Coherently, the transmitted THz electric field is measured as a function of time to obtain a time-domain signal which is converted to noise-free frequency-domain signal using Fourier transformation function.

THz-TDS is a non-contact, non-invasive and label-free detection technique and is extensively applied in biomedical imaging. However, THz-TDS has proved to be less sensitive for detection of micro-organisms (like yeast, molds, and bacteria) of size equal to or less than $\lambda/100$, due to their transparency under THz frequencies. Recently, plasmonic nanoantennas and metamaterials have proved to be effective devices for detection of micro-organisms, organic- and biomolecules. These devices show resonances with strong field enhancement across the gap in the THz frequency range, which is highly sensitive to changes in dielectric constant of the gap region. Therefore, these devices are used as biosensors for ultra-sensitive and label-free detection of micro-organisms, organic- and biomolecules. In this section, we discuss the two widely used label-free THz-TDS methods: (i) THz-TDS using molecular dynamic (MD) simulations, and (ii) THz sensing by nanoantennas and metamaterials.

Figure 12. Spectral analysis for identification of biomaterials. (A) Distinct spectral signatures can be used to discriminate a bacterial cell, spore and intracellular metabolite. (B) Bacterial species can be differentiated from their differences in THz optical constants. (C) Resonant frequency shift analysis using THz nanoantenna biosensors can be used to study the presence of biomaterials. Adapted with permission from Ref. © 2016, Springer Nature.

Figure 13. Conventional THz time-domain spectroscopy setup developed by Grischkowski et al. Adapted with permission from Ref. © 2016, Springer Nature.
A significant number of MD-based computational analysis have been performed to interpret the THz absorption spectra of protein solutions. Many studies showed the anomalous dynamics of water in the hydration shell due to the fact that surrounding water molecules were heterogeneously perturbed by the solute. Bandyopadhyay et al. have performed a significant amount of MD simulations to study the effects of hydration of protein molecules. Various methods have been used to study the thickness of villin headpiece sub-domain HP-36 which includes MSD, velocity autocorrelation function analysis, H-bond time correlation function analysis and reorientational correlation function analysis of water molecules. According to the simulation results, the different helical segments had a heterogeneous influence on the water dynamics, which were limited to the first hydration layer. Some similar results were obtained in which it was demonstrated a clear distinct power spectrum (VDOS) for water molecules bonded to different planes of antifreeze protein by hydrogen in the spectral domain of 1-4 THz. While studying the vibrational spectrum of water in the villin headpiece subdomain hy-
dration layer, O···O bending mode showed a blueshift in the first hydration layer, which is noticed for water molecules bonded to protein by hydrogen. It also showed the possibility of the structural flexibility of protein. Later an atomistic MD simulation of hen egg-white lysosome solvated in explicit water molecules at room temperature was performed, which reported that a few large-amplitude bistable motions exhibited by two coils controlled the overall flexibility of protein molecules. A series of MD simulations were performed to compare the experimental data of far-infrared spectroscopy used to study the dynamics of three aqueous peptides with varied helicity. Using the first principles, extensive studies on water, resolved in time and space, reported that the group motion of H-bonded molecules in the second solvation shell significantly contributed to the absorption at about 2.4 THz, also showing the presence of third-shell effects. Heyden et al. in their future publication showed the capability of nonpolarizable water models in reproducing low-frequency, inter-molecular vibration of water since electronic polarization is dominated by the static molecular dipoles. The depth of hydration shell in the hydrated lysosome, BPTI, TRP-cage, and TRP-tail was estimated using MD simulations.

To perform a basic MD simulation of a molecule, first and foremost a force field must be applied to characterize the molecular interaction of the molecules. In the next step, the molecule is positioned in a unit cell of desired shape and size followed by the addition of water molecules, known as solvation step. Then ions are added to neutralize the net charge of the system. After the addition of ions, the system is then relaxed through a process known as energy minimization. This process also ensures that the system is free from steric clashes or inappropriate geometry. For further simulation, the system needs to be brought to the desired temperature. After attaining the desired temperature, an adequate amount of pressure must be applied until it reaches a proper density. This whole process is known as equilibration and is conducted in two phases. The first phase is conducted to attain the desired temperature under NVT (constant Number of particles, Volume, and Temperature) or isothermal-isochoric ensemble. The second phase is conducted to stabilize both pressure and density of the system under NPT (constant Number of particles, Pressure, and Temperature) or isothermal-isobaric ensemble. After attaining the desired temperature and pressure, the system is finally ready for the MD simulation, known as MD production run. After performing the final MD-run, the system is ready to be analyzed. From MD simulation, the time-dependent properties are obtained via. correlation function, like velocity autocorrelation function (VACF). The time-domain properties are then converted to frequency-domain properties using Fourier transformation function, for example, the vibrational density of states (VDOS). The whole MD simulation steps are summed up in a flowchart (Fig. 14).

Fig. 15 (A) shows the MD simulation generated VACF curves for oxygen and hydrogen atoms in bulk water and in the water within 3 Å of lysosome molecule (first hydration layer). The figure depicts two results: i) The hydrogen dynamics get uncorrelated faster (0.85 ps earlier) than oxygen dynamics, and ii) The dynamics of the oxygen atoms are much more restricted in the first hydration layer than in bulk water (as compared from their extremums) due to caging-effect. The corresponding VACF data was further Fourier transformed to get a set of VDOS data as shown in Fig. 15 (B). In the figure, at 1.1 THz a well-defined peak is shown by the oxygen atoms of bulk water signifying the bending motion of O – O – O atoms (known as triplets of H-bonded oxygen atoms). But in the case of lysosome-bounded water molecules, this peak is blue-shifted by 0.4 THz signifying that the H-bonds between O atoms gets stronger in the hydration layer. This peak has a lower amplitude compared to that of the oxygen atoms of bulk water, as the presence of lysosome does not have much influence on the vibrational mode of water molecules. The VDOS of hydrogen in both situations is very flat as they are not much influenced by the protein molecule. The absorption spectrum can be solved by applying Fourier trans-
Figure 17. Interpretation of nanoantenna enhanced THz interactions of biomaterials using FDTD method. (A) Schematic of the cross section view of a metallic nanogap cladded with an absorptive homogeneous dielectric film with complex refractive index. (B) Normalized transmittance simulated by varying the imaginary part of the complex refractive index of the homogeneous dielectric film. (C) Transmittance peak values and resonance frequencies are plotted for various complex refractive indices. Adapted with permission from Ref.23. © 2018, De Gruyter.

\[
\alpha(\omega) = \frac{1}{4\pi \epsilon_0} \frac{2\pi \omega^2}{3k_B T \left| n(\omega) \right|} \int_0^\infty e^{i\omega t} \left\langle M(0)M(t) \right\rangle dt \tag{27}
\]

here, V denotes the volume of the system, \(k_B\) denotes the Boltzmann’s constant, T denotes the absolute temperature of the system, c denotes the speed of light and \(n(\omega)\) denotes the frequency dependent refractive index.

Figure 18. Effects of various gap-widths on THz-sensing of RDX molecules. (A) Schematic of the cross section of a THz single-slot nanoantenna containing RDX molecules. (B) Absorption spectrum of RDX molecules (1 mg) onto the bare quartz substrate. (C) Absorption coefficients peaks and cross section of RDX molecules in various nanoslot gap-widths \(w\). The black dashed line signifies the \(1/w\) dependence. Reprinted with permission from Ref.89. © 2013, American Chemical Society.

Figure 15 (C) is the absorption spectra of bulk water obtained experimentally (black line)237 and by MD simulation (red line),238 describing the inter-molecular hydrogen bond collective modes.

B. THz-Nanoantenna and Metamaterials Sensing of Micro-organisms, Organic- and Biomolecules

THz nano-structures can be used for ultra-sensitive, label-free and non-invasive sensing of molecules and
biomaterials. As discussed earlier in this section, the strong THz field enhancement along with resonances in the gap region of these nano-structures are sensitive to the changes in the dielectric constant of the insulating gap material. If the gap is filled with desired biomaterial sample, due to enhanced THz-interaction, the dielectric (i.e., the biomaterial sample) will show an enhanced THz-absorption therefore, the THz optical properties can be studied from the THz dielectric response. Thereby, making the necessary change in the THz-TDS setup (Fig. 16), enables enhanced sensing of molecules and micro-organisms which were not sensed by conventional THz-TDS setup. Therefore, from the Fourier transformed spectra (frequency-domain amplitude and phase) obtained from the sample and reference transmitted signals, the complex optical properties are computed from the following relation:

\[ A_s(\omega) = A_r(\omega) \cdot e^{-\left(\frac{\alpha(\omega)}{2}\right)} \cdot e^{i\phi_r n(\omega) d} \]  \hspace{1cm} (28)

where, \( A_s \) and \( A_r \) are the amplitudes of sample and reference transmitted signals, respectively. The real parts of the absorption coefficient and the index of refraction are denoted by \( \alpha(\omega) \) and \( n(\omega) \), respectively, and thickness of the dielectric is denoted by \( d \). The real part of refractive index \( n(\omega) \) is given by

\[ n(\omega) = 1 + \frac{(\phi_r - \phi_s)c}{2\pi df} \]  \hspace{1cm} (29)

and applying Beer-Lambert law, absorption coefficient is given by

\[ \alpha(\omega) = \frac{2}{d} \ln(T) = \frac{2}{d} \ln \left( \left( \frac{A_s(\omega)}{A_r(\omega)} \right)^2 \right) = \frac{4\pi fk}{c} \]  \hspace{1cm} (30)

where, \( \phi_r \) and \( \phi_s \) are the phases of sample and reference transmitted signals, respectively, \( T \) denotes the transmittance and \( f \) is the frequency of the input THz-signal.

Through FDTD simulation, an intense study of this biosensing process can be done. The biomaterial sample film is assumed to be a homogeneous dielectric film of a thickness proportional to the molecular concentration, is sandwiched between two gold films (Fig. 17 (A)). The dielectric film has a complex refractive index \( A \cdot n + iB \cdot \kappa \), where \( A \) and \( B \) are constants whose values range from 1.0 - 3.0 over a frequency band. The absorptive dielectric film was inserted in the gold nanogap by applying an auxiliary differential equation. To study the electric field interaction in the absorptive dielectric film, a non-uniform mesh was applied over the whole film with the smallest step-size of 10 nm. To the nanoan-
Figure 20. Highly-sensitive and selective nanoantenna. (A) Schematic of a THz nanoantenna for detection of sugar molecules. (B) Fructose antenna with stains of 250 mg/dL fructose (top-right) and D-glucose (bottom-left). (C) THz transmittance through stained fructose antenna illustrating the selective nature of nanoantenna. (D) THz transmittance peaks of fructose and D-glucose at different concentrations using fructose antenna. (E) THz transmittances of added sugars and artificial sweeteners in various branded beverages and dietary sodas using a fructose antenna. (F) THz absorption coefficients of low-concentrated artificial sweeteners: Acesulfame K and Aspartame. Reprinted with permission from Ref. 88. © 2015, Springer Nature.

A highly-sensitive and selective nanoantenna, THz electromagnetic waves are made to be incident normally. As the THz waves pass through the dielectric film, the transmitted THz-electric field decays exponentially and is given by

$$T_s(\omega) = Ce^{-\kappa k(\omega)h}$$

here, $T_s = (E_s(\omega))^2$ and $T_r = (E_r)^2$ are the transmittances through dielectric and air nanogaps, respectively. In the above relation, C is known as the transmittance ratio at the air-dielectric interface, $k = \frac{2\pi f}{c}$ is known as the incidence momentum and h is the thickness of the dielectric. Fig. 17 (B - C) shows the simulated transmittance for different complex refractive indices. It is evident from the figure, that the absorption is dependent on the imaginary part of the complex refractive index ($\kappa$), and the resonance frequency is solely dependent on the real part of the complex refractive index (n). However, the change in resonance frequency is quite small but stronger absorption can lead to an appreciable change. Therefore, the variation in the transmission spectra will provide evident proofs for identification of molecules and species contained in the biomaterial sample.

To study the effects of various gap-widths on THz-sensing, a single-slot THz nanoantennas of length 90 µm and slot-widths of 50 nm (50 nm thick), 100, 200, 500, 1000 and 5000 nm (100 nm thick) was fabricated on a thick quartz substrate and filled with 1 mg/ml RDX (1,3,5-trinitrohydro-1,3,5-triazine) molecules. Initially, the THz-absorption ($\alpha$) of 1 mg RDX molecules placed over a bare quartz substrate was studied which is shown in Fig. 18 (B). Then the absorption of RDX molecules inside the various nano-slots was studied and the data obtained was plotted against the slot-widths as shown in the Fig. 18 (C). From Fig. 18 (B - C), it is evident that nanoantenna enhances the THz-absorption by a large factor of $10^3$.

The effects of different substrates on biomaterial detection were studied using THz-antenna (length = 100 µm) with $10 \times 10$ slot-array each with a slot-width of 2 µm and periodicity of 200 µm (Fig. 19 (A - B)), was lithographed using electron-beam on two different substrates, Si (undoped) and quartz, to sense yeast samples. Using FFT (Fast Fourier Transform) algorithm, the normalized THz-transmission amplitudes for THz slot-antenna, with (an average of 50 yeast molecules, or $N_{av} = 50$) and without yeast sample was analyzed (Fig. 19 (C)). From the figure, an evident 9 GHz red-shift was observed in the resonance frequency. To com-
Figure 21. Detection of virus samples using THz nanoantenna sensing chip. (A) Schematic of a THz nano-slot antenna array sensing chip used to detect virus samples in liquid state. (B) Transmittance spectra measured using a multi-resonance nanoantenna, with and without H9N2. (C) Difference in transmitted intensity ($\Delta T$) and resonance frequency shifts from each fundamental resonance peak ($\Delta f$) for H9N2 virus sample. (D) THz transmission spectra through single-resonance nanoantenna, with and without virus samples (H1N1, H5N2 and H9N2). (E) Difference in transmitted intensity ($\Delta T$) and resonance frequency shifts from the fundamental resonance peak ($\Delta f$) of single-resonance nanoantenna for different virus samples. Reprinted with permission from Ref. 92. © 2017, Springer Nature.

To compare the effects of different substrate, the normalized THz-transmission amplitudes were measured for Si- and quartz-substrate THz antennas as shown in Fig. 19 (D - E). Comparing the measured amplitudes, quartz showed stronger red-shifts compared to Si-substrate (Fig. 19 (F)), showing $1/\varepsilon_{eff}$ dependence of the resonant frequency-shift ($\Delta f/f_0$), where $\varepsilon_{eff} = n_{eff}^2$ is known as effective dielectric constant. Hence it can be concluded that by using low dielectric constant substrate, the sensitivity of a THz nanoantenna can be enhanced.

THz nanoantennas are also selective in nature. This selective detection was shown using a nanoantenna of length 35 $\mu$m having a resonance frequency of 1.7 THz. This antenna was specially designed to differentiate between fructose and D-glucose, and is also known as fructose antenna (Fig. 20 (B)). These molecules were discriminated from their measured transmittances using the fructose antenna as shown in Fig. 20 (C - D). Using the same nanoantenna, the sugars and low-concentrated artificial sweeteners (acesulfame K and aspartame) contained in beverages and dietary sodas, respectively, of popular brands were detected. The detection of these artificial sweeteners is important as these are recently found to be addictive and toxic in nature. The different transmittances of sugars contained in sweetened beverages of various brands in the THz range (0.5-2.5 THz) are shown in Fig. 20 (E). The low transmittances seen in the figure are due to the two artificially added sweeteners whose THz-absorptions is shown in Fig. 20 (F). Hence, nanoantennas can provide highly sensitive detection even at low molecular concentration.

Recently, Lee et al.92 studied the THz-transmittances of various virus samples (H1N1, H5N2, AND H9N2) using two THz nanoantennas: i) multi-resonance nanoantenna (with resonance frequencies of 0.63, 0.93 and 1.31 THz), and ii) single-resonance nanoantenna (with resonance frequency of 1.4 THz), which are shown in Fig. 21 (B - E). Similar work has been reported by Park et al.94 in which they studied the transmission amplitude in both presence and absence of virus samples (PRD1 and MS2 viruses) using a THz nanogap metamaterial (Fig. 22).

V. CONCLUSION AND FUTURE OUTLOOK

THz waves are less penetrating and non-ionising electromagnetic waves. These waves are also known as ‘sub-millimeter waves’ and hence, is widely used in the fields of astronomy and spectroscopy. Since the description of electromagnetic interactions with metal is elucidated by using Maxwell’s equations, researchers are
very much fascinated to study the electric field localization and other plasmonic effects in various metallic nanostructures. Numerous investigations reported that the electromagnetic interactions with metal film increase the mobility of charges in the film, tending it to move towards the metal edges, leading to the enhancement of the electric field inside different nanogap structures. To study the light-matter interactions, researchers are fascinated towards THz waves as they can squeeze through sub-nanometer metallic gaps (THz nanoantennas) and show non-linear optical responses. These nanoantennas are further integrated with different materials to study its novel plasmonic properties. Recently, successful fabrication of graphene-integrated plasmonic system\textsuperscript{70,167,239-242} has boosted further investigations on their plasmonic properties because graphene is atomically thin and is electrically tunable.

As discussed earlier in this review, THz nanoantennas have played a crucial role as biosensors for ultra-sensitive detection of various biomolecules and biomaterials, which is our prime focus in this review. We have come across various literatures in which we have seen the development of nanoantennas, becoming more sensitive and selective. Due to its enhanced detection in low molecular concentrations, in future nanoantennas can be used to monitor blood sugar level.\textsuperscript{88} As an emerging future technology, nanoantennas can be used for early detection of cancerous tumours\textsuperscript{243,244} which will lead to the development of effective cancer treatment. Few recent works have shown that biosensing based on surface plasmon resonance (SPR) has proved to be effective in label-free tumor detection\textsuperscript{245-248} and can be used to detect a single molecule of an early stage tumor. Currently, research and development are in progress in making a nanoantenna based SPR biosensor which will be able to detect cancer cells at an early stage.

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VII. CONFLICT OF INTEREST

The authors declares no conflict of interest.

VIII. KEYWORDS

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