Optics Communications xx (xxxx) xxxx–xxxx

Contents lists available at ScienceDirect

Optics Communications

journal homepage: www.elsevier.com/locate/optcom

Real-timely monitoring the interaction between bovine serum albumin and drugs in aqueous with terahertz metamaterial biosensor

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ARTICLE INFO

Keywords:
Metamaterial
Biosensor
Bovine Serum Albumin (BSA)
Real-timely monitoring
Terahertz spectroscopy

ABSTRACT

In this paper, a metamaterial (MM) resonator used as a sensitive biosensor is designed and fabricated for monitoring the interaction between bovine serum albumin (BSA) solution and four kinds of drug solutions in real time. The transmission spectra of the resonator are simulated and measured with terahertz time-domain spectroscopy system where the distinct resonance frequency shifts are observed. The experimental results indicate that the interactions between BSA and every kind of solution are violent before the reaction reaches equilibrium, and the reaction solutions manifest varying permittivity. Moreover, different reaction solutions show different frequency shifts and reaction times. The MM resonator worked as an effective biosensor achieves to monitor the interaction between BSA and drug solutions in real time, which is very useful for the development of novel drugs and other biomedical applications.

1. Introduction

Terahertz (THz) wave is the electromagnetic wave between the microwave and infrared. Since the energy of THz photon is lower than that of visible light and X-ray, it would not cause ionization to biological molecules, tissues and organs, and has potential application in the field of biosensing and biomedicine. Low-frequency collective vibrational modes of biomolecules was examined [1] using THzpulse spectrum, and the broadband absorption increasing with frequency was observed for lyophilized powder samples of calf thymus DNA, bovine serum albumin (BSA) and collagen in the 0.06–2.00 THz frequency range. The usages of THz time domain spectroscopy (THz-TDS) for studying conformational flexibility and conformational change in biomolecular has been discussed [2]. Previous results indicated that THz-TDS has prominent performance in identifying biomolecular species, conformational state, mutation of biomolecules, and so on.

Metamaterials (MM) are artificial electromagnetic (EM) materials and media [3] which have exotic EM responses not available in nature; they consequently have many applications, such as negative refractive index materials [4], superlenses [5], cloaking [6] and resonance absorbers [7]. Recently, with rapid development of THz technology and micromachining technology, many THz functional devices, such as tunable filters [8], biosensors [9] and resonators [10], are emerged. For all these devices, MM based THz resonators show enormous potential in the fields of biomedicine, because they have four distinct advantages: 1) high sensitivity and high quality factor; 2) less sample consumption; 3) label-free detection without addition of other reagents; and 4) fast response and simple measurement.

In the past decade, many groups engaged in this area. The sensitivity of split-ring-resonator (SRR) based biosensors fabricated on different substrates was studied [11], and the researchers found that SRR fabricated on ultrathin silicon nitride substrate showed higher sensitivity and better performance. In addition, a paper-based MM device was proposed [12], and proof-of-concept demonstrations were accomplished by patterning micrometer-sized MM resonators on paper substrates, and the resonance shift induced by varying concentrations of glucose solution on the paper MM was monitored. Label-free monitoring of interaction between DNA and oxaliplatin in aqueous solution [13] was conducted using SRR with THz-TDS. Then, a SRR based highly-sensitive, label-free and specific biosensor [14] was demonstrated to recognize streptavidin-agarose and a redshift of

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http://dx.doi.org/10.1016/j.optcom.2016.11.006
Received 27 July 2016; Received in revised form 13 October 2016; Accepted 3 November 2016
Available online xxxx
0030-4018/

6.76 GHz was measured at high resonance frequency. In addition, all-dielectric MM sensor presenting fano-type resonance [15] was fabricated.

BSA is the most abundant protein in blood and can easily combine with many endogenous and exogenous compounds. Moreover, it is an important target of many drugs due to its capability of testing and valuing the practical effect of the drugs. Therefore, monitoring the interaction between BSA and drugs in aqueous is very helpful for studying the reaction process of the drugs in the body, and thereby provides scientific guide for medicine giving and therapy. Many methods, such as fluorescence spectroscopy [16], infrared spectroscopy [17] and ultraviolet spectroscopy [18], have been attempted to analyze the mechanism of reaction between BSA and drug solutions, but the efficiency is low. A polarization-insensitive MM biosensor composed of metallic square ring resonator was proposed [19] to detect the concentration of BSA solution, and the detection limit of 17.7 μmol/L was demonstrated. However, highly effective real-time monitoring of the interaction between BSA and drug solutions is still challengeable.

In this paper, MM THz resonator is introduced to monitor the interaction between BSA and four kinds of drug solutions in real time. Since the resonance peak of MM resonator is very sensitive to the change of permittivity of the dielectric on its surface, the interaction between BSA and four different drug solutions: Roxithromycin (RM) solution, Norfloxacin (Noroxin) solution, Ciprofloxacin (CPFX) solution and Cephradine (CF) solution can be efficiently detected. The reaction processes are monitored utilizing the analysis of the resonance frequency shift and the permittivity of the reaction solutions. The MM biosensor realizes sensitive real-timely monitoring of the interaction between BSA and drug solutions, which is significant in biomedical applications.

2. . Design and simulation of MM resonator

As shown in Fig. 1, the unit cell of MM resonator is a square with length of side a 80 μm, and it consists of an aluminum SRR and an aluminum bar resonator on the high resistance silicon substrate. The other structure parameters illustrated in Fig. 1(a) are b=12 μm, c=8 μm, d =15 μm, e =55 μm and f =40 μm, respectively. The thickness of the metallic layer is 0.1 μm, and that of the silicon substrate is 350 μm. The THz wave is polarized along y-direction and normally incident to the surface of the MM resonance.

The MM resonance is simulated and optimized using commercialized full-wave EM simulation software CST Microwave Studio 2013 [20] which based on finite-differential-time-domain (FDTD) method. For a single unit cell shown in Fig. 1(b), open boundary condition is set in the z direction, and the unit cell boundary conditions are set in the x and y directions, respectively. The metallic (aluminum) layer is modeled as lossy metal with an electric conductivity [20] σ=3.57×10^{7} S/m. The high resistance silicon substrate is modeled as normal material [20] with a real part of permittivity ε=11.7 and an electric conductivity σ=2.5×10^{-4} S/m.

When the top surface of the MM resonance is covered with a layer of 350 μm-thickness dielectric (describing the reaction solution in our experiment) with different permittivity ε_r, i. e., ε_r=1, 2 and 3, the corresponding transmission spectra are plotted in Fig. 2(a). As we can see, the resonance frequency of the MM resonator is around 0.9 THz and undergoes redshift with the increasing of the permittivity of the dielectric ε_r. This evidences that the MM resonator is very sensitive to the change of its surface environment. In addition, there is only one resonance located in the frequency range of 0.4–1.2 THz, where the effective spectral range covers in our experiment. Therefore, the MM resonator is a good option for biosensor devices. The calculated surface current distribution at 0.9 THz for ε_r=1 is illustrated in Fig. 2(b). The surface current strongly oscillates on the surface of the two arms in SRR, where induces a typical electrical dipole resonance. This dipole resonance produces the main losses of the metamaterial structure, and it can be equivalent a LC resonance whose resonance frequency f is given by [21]

$$f = \frac{1}{2\pi\sqrt{L_e C_e}} \tag{1}$$

where L_e is the equivalent inductance, and C_e is the equivalent capacitance of each arm of SRR which is proportional to the permittivity of the dielectric ε_r on the surface of the resonator.

3. . Experiment

After verifying the performance of the MM resonator in simulations, we fabricated the sample using a surface micromachining process. Firstly, a layer of photoresist is coated on the surface of high resistance silicon substrate by spinning. After the process of ultraviolet exposure and developing, the MM resonator pattern is formed on the high resistance silicon substrate, and then a layer of Al film is deposited on the surface. Lastly, a lift-off process is used to form metal MM resonator structure. The photograph and cross-section view of holding box are presented in Figs. 3(a) and (b), respectively. A plastic O-ring is used to prevent spillage of reaction solution. The micrograph of the fabricated resonator array and a unit cell are show in Fig. 3(c) and (d), respectively. The dimension of the matrix used for the experiment is about 8 mm×8 mm. Due to the diameter of the THz beam at the focus is about 4 mm, the effective dimension of the matrix is about 4 mm×4 mm.

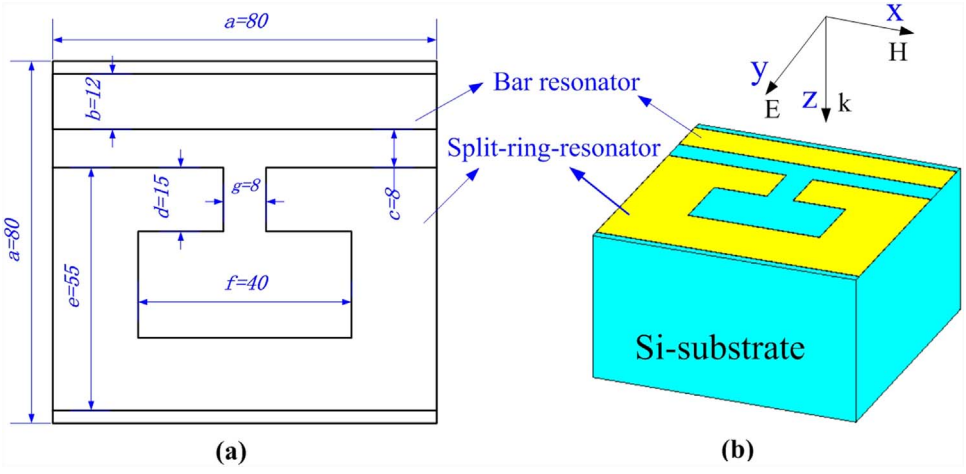

Fig. 1. (a) Top-view and (b) diagram of a unit cell of the MM resonance.