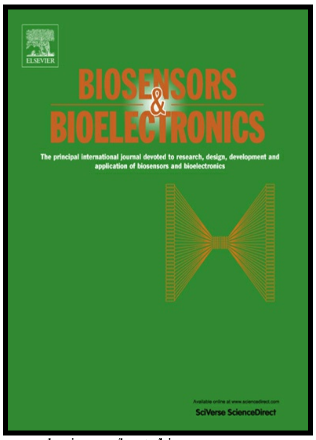

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Recent advances in the Metamaterial-inspired biosensors

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ABSTRACT
Metamaterials (MM)-inspired microwave biosensors are a valuable addition to the field of diagnostic approaches and prognostic tools. The fundamental principle behind these biosensors is unique dielectric signatures corresponding to healthy/diseased tissues. Relying on nonionizing radiation and offering an increased resolution with accuracy comparable to that of ultrasound devices, they are an attractive solution for noninvasive and label-free biosensing applications. High-quality-factor MM-inspired resonators are integrated with microfluidics to accelerate the lab-on-chip and point-of-care diagnostic approaches owing to the small detection volume and overall compact size of these devices. A variety of biomolecular detection, glucose detection and hyperthermia treatment using state-of-the-art MM-inspired biosensors have been discussed. Optical transduction techniques (e.g., surface plasmon resonance) which enhance the sensitivity in terms of limit-of-detection and resolution, have also been outlined. Utilization of microwave biosensors as therapeutic agents is at its initial stages owing to lack of required sensitivity and reliability in recently proposed MM-inspired biosensors.

Keywords:
Metamaterials, Microwave, Biosensor, Terahertz, Dielectric, Plasmon

1. Introduction

High-frequency electromagnetic (EM) waves (GHz regime) have potential to cross the capacitive barrier of the cell membrane and may interact with the cytoplasm, consequently providing a rich interaction in what is known as γ-dispersion (Artis et al., 2015).

Metamaterials (MM) are artificially synthesized structures with average sizes smaller than a quarter wavelength ($\lambda/4$) and are known to exhibit extraordinary properties (Caloz and Itoh, 2006). For instance, a MM-inspired chemical sensor resonating at $\lambda/12$ (Rawat et al., 2014), and a MM-inspired biosensor resonating at $\lambda/15$ (Lee et al., 2010), have been proposed. They exhibit high-quality-factor and small form factor whilst constructed from an easy design process and offering an inexpensive fabrication. Quality factor (Q) defines the sharpness of resonance and mathematically it is defined as the ratio between the resonance frequency (f_o) to the 3-dB bandwidth (Δf_{3dB}) (Pozar, 1998). High Q indicates the lower rate of loss as compared to energy stored in the cavity/resonator and vice versa. Using microfluidic systems, excessive waste of chemicals can be avoided, and an increase in yield is achieved in comparison with conventional methods in biochemistry, which utilize glassware at millimeter scale to handle fluids (Lee et al., 2014). The attractive features of RF resonators (e.g., non-invasiveness, small detection volume and rapid detection) are pronounced when integrated with microfluidics.

1.1. Physics of Metamaterials and sensing mechanism

The electromagnetic response of a material is changed according to the incidence of a wave, and two fundamental parameters govern this change, namely, permittivity (ε) and permeability (μ). These are a material's intrinsic properties; they are unique for every material owing to singular atomic configurations (Roychoudhury et al., 2016). The properties of a MM structure behave differently from those of its constituent materials, where each unit cell individually behaves as an electric dipole. MM structures simultaneously exhibit negative permittivity and permeability (Kim and Lee, 2016).

The principle of operation of MM-inspired sensors is based on the change in reflection/transmission coefficients (scattering parameters, S_{11}, S_{21}), which is induced in the sensed parameters (dielectric change) owing to variations in the permittivity, permeability, or refractive index of the MM-based resonator.

1.2. Common configurations of Metamaterials structures

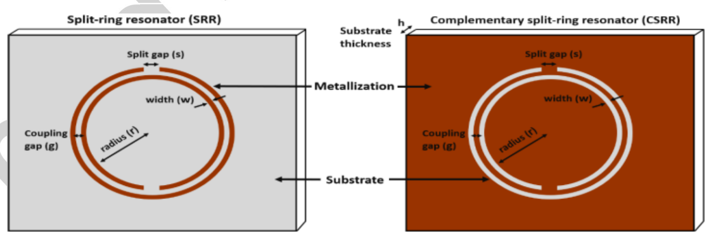
Split-ring resonators (SRR) and complementary split-ring resonators (CSRR) are the two most commonly used topologies of MMs. An SRR can be realized on the surface of a substrate, and it consists of a ring-shaped metallic pattern that provides inductance and the narrow opening gap that provides a high capacitance. A CSRR is a dual SRR structure, which can be realized by etching out a ring shape pattern from copper cladded on a substrate surface. A MM unit cell can be excited in several ways, for instance, a time-varying magnetic field can generate current loops in a MM unit cell if it is applied parallel to the ring axis. The operating frequency of these resonant elements can be tuned by adjusting the geometrical parameters as mentioned in Fig. 1 (a, b) (Salim and Lim, 2018).

2. MM-inspired biosensors (GHz domain)

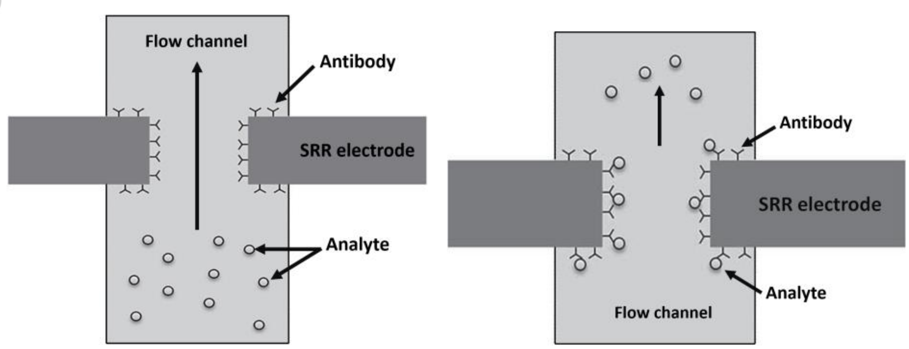
2.1. Biomolecular detection

MM-inspired biosensors that rely on affinity binding are becoming popular. In a bio-recognition process, first biomolecules are immobilized (ligand) on the sensor surface, and then the analyte to be detected is flowed through the sensor surface to selectively interact with the already-immobilized biomolecules (Vachali et al., 2015), see Fig. 1 (c, d).

In the period from 2008 to 2014, several MM-inspired RF biosensors based on affinity binding have been developed (Lee et al., 2010), (Lee and Yook, 2008), (Lee et al., 2011), (Lee et al., 2012), (Torun et al., 2014). For instance, the process of affinity interaction was employed on a sensor surface at the most sensitive location of the SRR (Torun et al., 2014). The surface treatments to immobilize the target biomolecules, additional coating of thin layers (gold, nickel) and a masking layer to bind the biomolecules were preconditioned. The target biomolecules with and without binding pairs were introduced on the sensor surface, and the frequency shift using these biosensors was reported in the range of 20 MHz to 150 MHz. A single SRR coupled with a high-impedance microstrip line (~80 Ω) was realized as a label-free biosensor (Lee et al., 2011), as shown in Fig. 1 (e). The affinity interaction between prostate-specific antigen (PSA) and its antibody (Cy3-protein G) has been investigated. A higher concentration of PSA resulted in a larger frequency shift. For instance, concentrations of 1 ng/ml, 10 ng/ml, and 100 ng/ml caused frequency shifts of 5 MHz, 10 MHz, and 20 MHz, respectively.

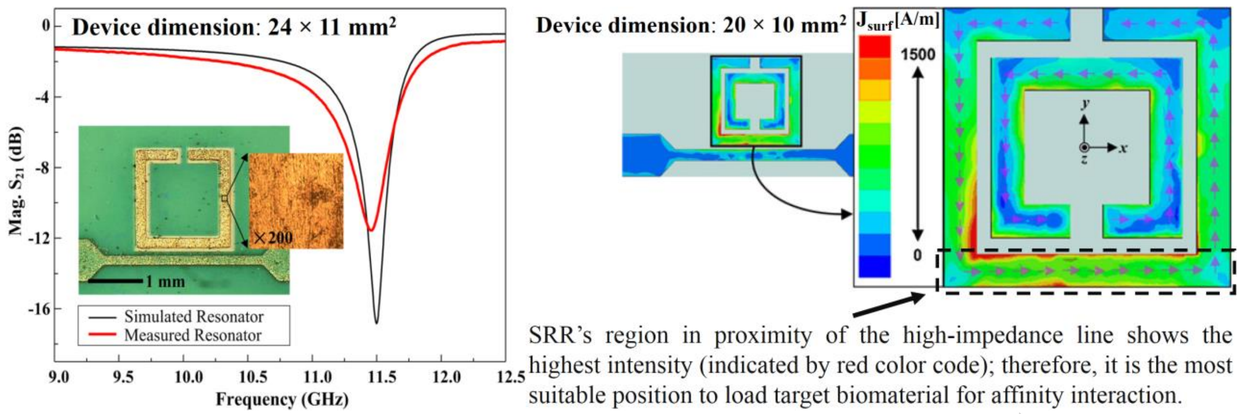


(a) (b)



(c) (d)

(e) (f)



To detect cortisol, high-impedance coupled-two SRRs have been realized as a label-free biosensor (Lee et al., 2012), Fig. 1 (f). Measurements showed 30 MHz and 20 MHz shifts in resonant frequency with respect to PSA and cortisol-coupled bovine serum albumin, respectively. In (Torun et al., 2014), a biosensor was introduced consisting of an SRR-based resonator with integrated monopole antennas. The affinity interaction between fibroblast growth factor 2 (FGF-2) and heparin was investigated. The device showed a sensitivity of 3.7 MHz/(µg/ml) corresponding to changes in heparin-concentration. The risk of contamination from the environment and the difficulty of accurately pouring the sample fluid on a precise position (a narrow region on the order of few 100s of µm or less) have been challenging concerns in these direct contact biosensors.

In (Jaruwongrungsee et al., 2015), a microstrip-coupled SRR structure integrated with microfluidics was proposed as a label-free biosensor. A shift in the resonance frequency of SRR around 6.5 to 13 MHz was measured by S_{21} when IgG binding was conducted on the SRR surface.

2.2. Glucose biosensor

In (Sathyanath et al., 2015), SRR- and CSRR-based microwave glucose biosensors were developed and the sensitivity was reported as 0.174 $MHz/mgml^{-1}$. In (Byford et al., 2015), a microfluidic multichannel resonator based on open split-ring resonators (OSRR) was proposed as a glucose biochemical sensor. Microstrip line coupled asymmetric OSRRs were realized to give rise to unique resonance in accord with each OSRR.

2.3. Hyperthermia treatment

The heating profile of biological tissues varies in relation to water content (Park, 2017). In addition, the absorption of a biological substance directly relates to its polarizability. In this context, two diamond-shaped resonators located on each side of an FR4 substrate were modeled (only simulation) to detect pig biological tissue (Sabah et al., 2015). The zeroth-order resonance (ZOR), a special category of MM, and shows unidirectional field distribution with almost uniform intensity (Baek and Lim, 2009). Homogenous heating to target cancerous tissues have been utilized in a ZOR-based MM resonator (Vrba et al., 2017). For instance, 25% SAR covering 84% of the treatment volume approaching 1 cm depth (test case) was observed (Vrba et al., 2017).

3. MM-inspired biosensors (THz domain)

Terahertz (0.1–10 THz) radiation has tremendous potential in the field of biomedical research (Yang et al., 2016) for many interesting applications. Optical transduction techniques such as, Surface plasmon resonance (SPR) and Localized plasmon resonance (LPR) enable monitoring of biomolecular binding events while avoiding labeling steps (which are time-consuming, expensive, and precision-interfering) (Kravets et al., 2013).

3.1. Plasmonic biosensors

SPR- and LPR-based MM-inspired biosensors are known to exhibit exquisite performance (excellent lower limit of detection (LOD), and resolution) when harnessed to trace the dynamics of low-molecular-weight biomolecules.

In (Chen et al., 2016), a terahertz label-free MM-based microfluidic biosensor was developed on polyimide and its sensitivity was reported as 3.5 THz/RIU.

To detect biological substances having low molecular weight, in (Zeng et al., 2015), a hybrid gold/graphene metasurface was proposed as a highly sensitive biosensor that can detect trace amounts of substances. A high sensitivity of 1×10^{18} M for cysteine-rich intestinal protein (8.5 kDa) was measured.

The resonance frequency of terahertz MMs is comparable with the vibrational frequency of some biomolecules, such as cancer biomarkers (Geng et al., 2017). Keeping in view this advantage, one-gap SRR- and two-gap SRR-based terahertz biosensors integrated with microfluidics have been proposed, as shown in Fig. 2 (a, b). Their primary function is to detect early-stage liver cancer biomarkers. The novelty of this biosensor is that it overcomes the absorption of water into the trace biomolecules.

To eliminate the sensitivity dependence specific to the infrared region and bulk Kretschmann configuration (Kabashin et al., 2009), an extremely sensitive plasmonic biosensor was proposed based on hyperbolic MMs, as shown in Fig. 2 (c, d) (Sreekanth et al., 2016). It was able to detect biomolecules with lower molecular weight, for instance, biotin with a molecular weight of 244 Da.

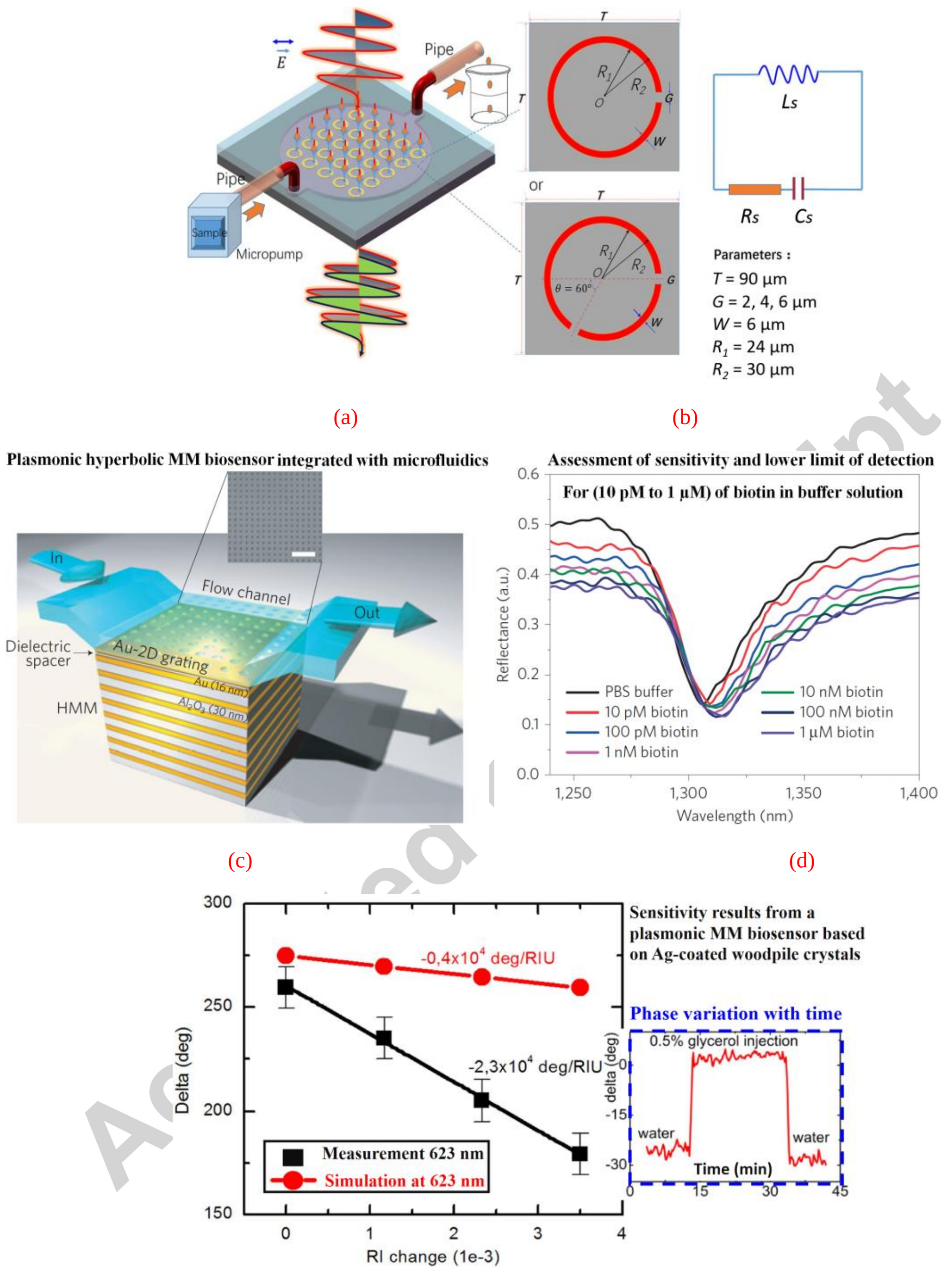


Fig. 2. (a) THz MM biosensor integrated with microfluidics. (b) RLCs equivalent circuit of the proposed SRRs with design parameters. Plasmonic hyperbolic metamaterial biosensor integrated with microfluidics. The assessment of sensitivity and lower limit of detection using lower-molecular-weight biomolecules. (c) 3D view of the plasmonic hyperbolic MM biosensor with a fluid flow channel. (d) Reflectance spectra of the sensor device for various concentrations (10 pM to 1 µM) of biotin in buffer solution for the first mode. (e) Assessment of sensitivity variation, represented by a change in refractive index due to the addition of various glycerol concentrations. The inset shows a typical phase variation Δ when 0.5% of glycerol is added to buffer solution.

Metasurfaces are constituted from periodic arrangements of MM unit cells; thus, a metasurface can act as an interface of discontinuity, causing abrupt changes in both the amplitude and phase of the incident wave. In (Chou Chau et al., 2017), a 2D array of crossing metal nanoparticle (MNP) thin film was proposed as an infrared plasmonic biosensor. The measured transmittance dips with an enhanced sensitivity range of 120 to 700 nm RIU^{-1}, corresponding to an ε range of 1.0 to 3.0 was observed.

In (Wang et al., 2016), a novel THz MM-inspired "polarization-insensitive" biosensor was developed by introducing a symmetric slit on each side of the SRRs, which showed a 275-GHz frequency shift for a 3 mmol/l aqueous solution of bovine serum albumin.

To further enhance the sensitivity, a 3D structure consisting of a photonic crystal MM has been proposed as a biosensor (Aristov et al., 2016). The 3D structure consists of a metal (Ag-coated woodpile crystals) and dielectric (gaps between the woodpile crystals) with a high surface-to-volume ratio, providing a very high sensitivity of 2600 nm per refractive index unit (RIU) when glycerine-aqueous solutions were tested, as shown in Fig. 2(e).

4. Results

MM-inspired biosensors exhibit adequate sensing capability (indicated by detection limits), which makes them a potential candidate for field applications. The detection limit and sensing schemes of various MM-inspired biosensors are presented in Table 1.

Table 1. Performance of various MM-inspired biosensors, exhibiting excellent detection limits.

Reference	Biosensing scheme	Bioanalyte	Operating frequency	Detection limit	Q-factor
(Lee et al., 2011)	SRR	PSA-antibody	11.5 GHz	1ng/ml	55
(Lee et al., 2012)	Double SRR	PSA-cortisol	10.2 GHz	100 pg/ml	50
(Torun et al., 2014)	SRR	FGF2-heparin	2.16 GHz	10 μg/ml	93
(Yan et al., 2016)	SRRs array	IgG	1-2 THz	1 μg/ml	N/A
(Geng et al., 2017)	Double splits SRRs	Alpha fetoprotein-Glutamine transferase isozymes II	0.5-1 THz	0.02524 μg/ml	N/A

5. Conclusion

RF technology has been well-established for the development of biosensors that can characterize biological cells in the microwave spectrum. Aside from miniaturization, MM biosensors show better sensitivity and its enhancement is continuing.

Microwave biosensors are a valuable addition to the field of diagnostic approaches and prognostic tools. The fabrication of novel structures that can provide enhanced performance is rapidly evolving and there is a growing trend of using scalable, low-cost fabrication methods that enabled utilization of flexible materials (e.g., elastomers as substrates) or paper as spacer/supporting substrates that can reduce the final cost (Lopez et al., 2017). However, there remains some challenges owing to difficulties in integration of several components into a single portable platform (Lopez et al., 2017).

It is hoped that a reliable biosensor can be developed that can not only non-invasively detect diseases and disease risks but also enable healthcare providers to inform patients at the point-of-care about the severity of affected/diseased cells and associated complications.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article contains additional figures and can be found online at:

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Highlights

State-of-the-art metamaterial-inspired biosensors are discussed in this comprehensive review.

- Commonly used materials and fabrication techniques for RF biosensors have been studied.
- Design strategies and simulation setup of RF biosensors have been studied.
- The most recent metamaterial-inspired biosensors have been reviewed by dividing GHz and THz domains.
- Finally, challenges and resolving strategies for metamaterial-inspired biosensors are discussed.