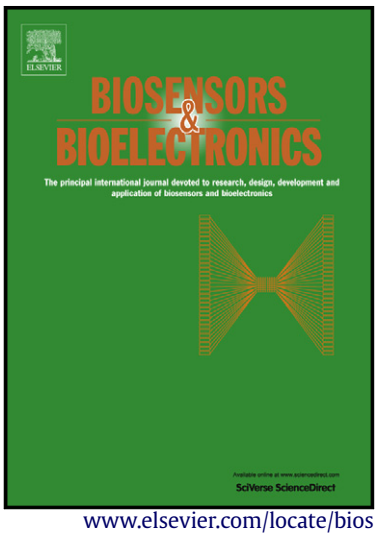

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www.elsevier.com/locate/bios

PII: S0956-5663(14)00358-3
DOI: http://dx.doi.org/10.1016/j.bios.2014.05.025
Reference: BIOS6787

To appear in: *Biosensors and Bioelectronics*

Received date: 27 February 2014
Revised date: 8 May 2014
Accepted date: 10 May 2014

Cite this article as: Hee-Jo Lee, Jong-Gwan Yook, Recent research trends of radio-frequency biosensors for biomolecular detection, *Biosensors and Bioelectronics,* http://dx.doi.org/10.1016/j.bios.2014.05.025

Recent research trends of radio-frequency biosensors for biomolecular detection

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Abstract

This article reviews radio-frequency (RF) biosensors based on passive and/or active devices and circuits. In particular, we focus on RF biosensors designed for detection of various biomolecules such as biotin-streptavidin, DNA hybridization, IgG, and glucose. The performance of these biosensors has been enhanced by the introduction of various sensing schemes with diverse nanomaterials (e.g., carbon nanotubes, graphene oxide, magnetic and gold nanoparticles, etc.). In addition, the RF biosensing

platforms that can be associated with an RF active system are discussed. Finally, the challenges of RF biosensors are presented and suggestions are made for their future direction and prospects.

Keywords: Biosensor, Biomolecule, Diagnosis, Radio-frequency, Detectable limit

Highlights

This paper reviews RF biosensors for biomolecular detection.
The representative RF biosensors are introduced and analysed.
The recently developed RF biosensors are estimated and analysed in detail.
The challenges of RF biosensors and their future direction are presente

Contents

Abbreviations: BSA, bovine serum albumin; cDNA, complementary deoxyribonucleic acid; CMOS, complementary metal oxide semiconductor; CNT, carbon nanotube; CPW, coplanar waveguide; CRP, cardiovascular reactive protein; DMM, digital multimeter; DNA, deoxyribonucleic acid; DUT, device under test; Hg, hemoglobin; IDCs, interdigital capacitors; GaRIgG, goat antirabbit immunoglobulin G; GNR, graphene nanoribbon; GO, graphene oxide; GOx, glucose oxide; GSG, ground-signal-ground; LOD, limit of detection; MNP, magnetic nanoparticle; MC, microcantilever; NanoMR, nanomechanical resonator; NFMI, near-field microwave imaging; NMR, nuclear magnetic resonance; PDAS, poly dimethyldiallyl ammonium chloride; POC, point-of-care; PSA, prostate specific antigen; QCM, quartz crystal microbalance; RFIC, radio-frequency integrated circuit; RFID, radio-frequency identification; RIgG, rabbit immunoglobulin G; RNA, ribonucleic acid; SAW, surface acoustic wave; SA, spectrum analyzer; SOLT, shot-open-load-through; SRR, split-ring resonator; ssDNA, single-strand deoxyribonucleic acid; TRL, through-reflection-load; VNA, vector network analyzer.

1. Introduction

In general, a biosensor can be defined as a device that incorporates a biological sensing element connected to a transducer (Eggins, 1996). As shown in Fig. 1, a biosensor is commonly composed of three parts: a detector, a transducer, and a signal conditioner. The detector part can be incorporated with sensitive biological elements such as enzymes, antibodies, nucleic acids, cell receptors, or microorganisms. The surface should be immobilized with a biological sensing element that can detect a specific analyte in order for the device to function as a biosensor. The transducer part converts an observable signal into a measured physical or chemical quantity, usually an electronic signal whose magnitude is proportional to the concentration of a specific chemical or set of chemicals. For this reason, biosensors can be categorized by diverse transducing mechanisms, such as optical, piezoelectric, electrochemical, and thermal effects (Chaubey and Malhotra, 2002).

[Fig. 1]

Similarly, RF biosensors can be employed with transducers of various RF device and circuit types, as shown in Fig. 2. In particular, these biosensors have been mainly based on resonator, which is a basic building block for implementing stop or pass band characteristics in the desired frequency region, as a transducer. In addition, a resonator can be utilized for accurate characterization of material parameters at specific frequencies (Chen et al., 2004). As summarized in Table 1, various resonators using mechanical, acoustic, and electromagnetic resonance have been widely investigated. For QCM (000) and MC devices (Bashir and Rashid, 2004), they recognize the mass difference as biomolecular binding by measuring the change in frequency from mechanical resonance. In particular, these sensing schemes are highly effective at determining the affinity of biomolecules to surfaces functionalized with recognition sites. And sensors based on nanoelectromechanical resonator (Arlett et al., 2011) are similar to the sensing principle of QCM and cantilever; they operates at low frequency region and are also required for very high-Q characteristic. On the other hand, electromagnetic resonators including

DR and SRR have been mainly designed and applied for biomolecular detection at high frequency region, i.e. microwave band. In case of a DR (Kajfez and Guillon, 1998), the microwaves are confined inside the resonator materials by the abrupt change in permittivity at the surface, and form standing waves in the resonator, oscillating with large amplitudes. As a result, the resonant frequency of DR is determined by the overall physical dimensions of the resonator and the dielectric constant of the material. For an example, RF biosensor with a high-Q DR allows observation of the small variation of the biomolecular concentration by measuring the shift of the resonance frequency and the reflection coefficient (Kim et al., 2008). In addition to the near field sensing scheme with a DR can image with and without the biomolecular binding as minute changes in the resonant frequency or Q-factor variation (Friedman et al. 2005). In recent years, a state-of-the-art RF biosensing platform – the miniaturized NMR system-based RF biosensor – has been developed for enhancing the performance of biomolecular detection via a RFIC technique (Sun et al., 2009). However, a novel RF biosensor still remains to be developed that has label-free and highly sensitive characteristics for use in biomedical as well as environmental applications.

[Fig. 2]

[Table 1]

In this review paper, we focus on the passive and/or active devices and circuits-based RF biosensors developed for biomolecular detection in the high frequency region, at a frequency range from 500 MHz to 50 GHz.

2. RF biosensors

2.1. Definition of RF biosensor and its elements

The RF terminology, ranging from 3 kHz to 300 GHz, encompasses all related entities such as materials, systems, devices, and circuits, used in wireless communication. In particular, the various RF devices and circuits, e.g. resonator (Lee et al., 2011, 2012, 2013), filter (Lee et al., 2008), RFID (Yuan

et al., 2013), as a transducer for high frequency RF biosensor are employed for biomolecular detection and then the biosensing information is recognized from suitable display equipment, such as VNA, SA, etc.. The representative RF biosensing schemes for detection of various biomolecules, including glucose, IgG, CRP, etc. and their performances are summarized in Table 2. According to the data, most RF biosensors have been mainly based on RF passive devices and circuits having a simple structure such as various types of resonators, TL, and IDCs. In recent years, active systems based on RFIC and/or hybrid PCB circuits have also been studied for biomolecular detection (Sun et al., 2009; Kim et al., 2013).

[Table 2]

2.2. Measurement system for RF biosensor

For a RF measurement system, first of all it must take a precise calibration such as SOLT, TRL and so on. In case of biosensors using RF passive devices and circuits, they can be simply measured by using a test fixture zig system connected with a VNA (Lee et al, 2008, 2010, 2011, 2012, 2013). Meanwhile, for the micro/nano-sized RF biosensors, more complex and elaborate measurement system is needed. Fig. 3 shows a schematic of a probe station system connected with a VNA for measuring a small sample. However, the measurement system is very expensive and bulky. On the other hand, the biosensing platform associated with RF active systems can easily perform measurements using simple and cost-effective equipment, such as DMMs (Kim et al., 2013).

[Fig. 3]

2.3. Sensing parameters of RF biosensor

As previously mentioned, RF biosensors have been mostly designed for creating stop or pass band resonance at a specific frequency. The resonant frequency of the S_{11}- and S_{21}-parameter (i.e., the reflection and transmission coefficient, respectively) can be sensitively changed with biomolecular binding steps and/or concentrations of the target biomolecule. Here, the *S*-parameter (or *S*-matrix) of a two-port VNA system can be expressed as

$$S = \begin{bmatrix} S_{11} & S_{12} \\ S_{21} & S_{22} \end{bmatrix}. \tag{1}$$

Physically, assuming that the DUT is symmetrical as well as reciprocal, the magnitude and phase of the complex *S*-parameter are given by

$$S_{11}(=S_{22}) = |S_{11}|e^{j\theta_{11}},\ |S_{11}| = 20\log\left(\frac{V_1^-}{V_1^+}\right),\ \theta_{11} = \theta_1^- - \theta_1^+, \tag{2}$$

$$S_{21}(=S_{12}) = |S_{21}|\mathrm{e}^{\mathrm{j}\theta_{21}},\ |S_{21}| = 20\log\left(\frac{V_2^-}{V_1^+}\right),\ \theta_{21} = \theta_2^- - \theta_1^+. \tag{3}$$

where V_1^-/V_1^+, V_2^-/V_1^+, and θ_{11}, θ_{21} are the ratio of reflected voltage wave to incident voltage wave of port 1, the ratio of transmitted voltage wave to incident voltage wave of port 2, and the corresponding phase difference, respectively (Lee et al., 2013). Of course, the measured *S*-parameter can be transformed into diverse sensing parameters such as capacitance (Lee et al., 2010) and impedance (Kim et al., 2008), as well as the Q-factor (Xu et al., 2010), etc..

2.4. Functionalization

In a biosensor, functionalization is a very important biological process for detection of a specific analyte. A RF biosensor is primarily carried out immobilization on the gold surface, like as typical biosensors, because the gold electrode is amenable to chemical surface modification and has excellent

stability. For an example, the gold surface binds with thiols with high affinity and it does not undergo any unusual reaction with them (Frasconi et al., 2010). Table 3 shows the surface modification of detector types for functionalization of RF biosensors. In particular, the simple biomolecular binding systems shown in Fig. 4(a), such as thiols (-SH)-linked biotin-streptavidin, and thiol-linked ssDNA-cDNA (Kim et al., 2013), is very useful for RF biosensor. Furthermore, the more complex biomolecular binding systems e.g., cys3-linked protein G-PSA-Ab (Lee et al., 2011), cortisol Ab-Ag (Lee et al., 2012), and alpha (α)-amylase Ab-Ag (Lee et al., 2013), can be also detectable, but the reproducibility of immobilization may be unstable compared to the simple biomolecular binding system. For functionalization of CNT-based RF biosensor shown in Fig.4 (b) (Lee et al., 2008), it is required for more complex process as following: first of all, a linker on the CNT surface via a non-covalent sidewall process is provided for functionalization and then a biotin is immobilized on the CNT and finally, streptavidin, target biomolecule, is bound to the biotinylated CNT (Chen et al., 2001, 2003). Therefore, the biological process of CNT-based RF biosensing scheme is somewhat time-consuming for detection of analyte.

[Fig. 4]

[Table 3]

3. Classification of RF biosensors

As mentioned earlier, the RF biosensors can be classified with transducers of various RF passive/active devices and circuits. In addition to these are used for a sensing part associated with active devices and circuits. In this session, the recently developed RF biosensors based on RF passive/active devices and circuits with or without nanomaterials are described with sensing principles and their pros and cons in detail.

3.1. Passive devices and circuits-based RF biosensors

3.1.1. SRR-based biosensor

Fig. 5 shows the schematic of an asymmetric SRR-based RF biosensor (Lee et al., 2013). It basically consists of a microstrip transmission line, which is a structure composed of a ground (metal)-substrate-signal line (metal) and a resonator. The resonator is excited by the time-varying magnetic field component of the microstrip line so that the surface current is induced on the resonator. Thus, the resonator produces a resonance at specific frequency to form a stopband characteristic.

[Fig. 5]

As shown in Fig. 6, the resonant frequency with each biomolecular binding step and α-amylase concentration is changed. This is because the input impedance (i.e., the resistance, inductance, and capacitance) of the resonator varies with immobilization of biomolecular concentration. From the resonant formula, the frequency shift can be approximately expressed as

$$f = \frac{1}{2\pi\sqrt{LC}} \approx f_0 - \frac{f_0}{2}\left(\frac{\Delta C}{C_0} + \frac{\Delta L}{L_0}\right) = f_0 - \Delta f. \tag{2}$$

where $L = L_0 + \Delta L$ ($L_0 >> \Delta L$), $C = C_0 + \Delta C$ ($C_0 >> \Delta C$), $f_0 = \frac{1}{2\pi\sqrt{L_0 C_0}}$, and $\Delta f = \frac{f_0}{2}\left(\frac{\Delta C}{C_0} + \frac{\Delta L}{L_0}\right)$.

Here, f_0 , L_0 , and C_0 are the resonant frequency, inductance, and capacitance of a bare resonator, respectively. In general, the S_{21} resonant frequency of resonators-based biosensing schemes are shifted toward the lower frequency region with biomolecular binding steps as well as concentrations (Lee and Yook, 2008; Lee et al., 2010, 2011, 2012). Especially, in case of RF biosensor having a simple and small resonator, it is very cost-efficient and easy of fabrication. Moreover, it consumes small specimen (~8 μl), and shows characteristic of rapid response. Above all, the sensing scheme can be easily designed for biomolecular detection at the desired or interested frequency region. However, the sensing device should be measured in dry state because solution effect is very dominant.

[Fig. 6]

3.1.2. IDCs-based biosensor

The IDC is a type of planar RF passive device, which can produce a relatively large capacitance due to its periodic metal-dielectric (air/SiO_2/Si) gap-metal configuration. The sensing scheme is a well-known transducer and is widely used at low frequency region (Mamishev et al. 2004). However, in high frequency region, as the frequency increases, the IDC device is transformed into inductance at a certain frequency, the so-called self-resonance frequency (SRF). So, the IDC device itself acts as a resonator at a specific frequency (Lee, Lee, Choi et al., 2010). In addition, to enhancement of the sensitivity and detectable limit of biosensors like as conventional biosensors, carbon nanomaterials (Yang et al., 2010; Shao et al., 2010) (e.g., buckyballs, CNTs, GNRs, and graphene, as well as GO) could be incorporated with IDCs device. The nanomaterials are biocompatible and well suited for detection of small biomolecules due to their large surface areas. For instance, RF biosensor based on IDC with a CNT is shown in Fig. 7 (Lee et al. 2008).

[Fig. 7]

[Fig. 8]Fig. 8 shows the change in frequency and Q-factor as biomolecular binding onto CNTs. Finally, when streptavidin is bound to the biotinylated CNTs, the frequency is dramatically shifted toward a lower frequency region, and simultaneously, the Q-factor of the sensor is more enhanced due to a decrease in the surface resistance resulting from increased passage of electrons through streptavidin-biotin binding. RF biosensors combined with GO (Yoon et al., 2013) has also been investigated recently for highly sensitive biomolecular detection scheme because the nanomaterial has a small size, large specific area, high mechanical strength, and high sensitivity to chemicals. In particular, GO (which is a single sheet chemically exfoliated from graphite oxide) is considered to be the most practical candidate for biochemical sensor applications because of its competitiveness in fabrication and its high affinity for biochemical materials (Liu et al., 2010; Dua et al., 2010; Zhu et al., 2010). As

before-mentioned SRR-based biosensor, the IDCs biosensing scheme has not only same advantages but also it can be easily combined with nanomaterials. However, the sample should be also dried for measurement like the SRR-based biosensor.

3. 2. Active devices and circuits-based RF biosensors

3.2.1. NMR-RFIC system-based biosensors

The miniaturized NMR-based biosensor shown in Fig. 9 was developed in 2009. The RF biosensor is based on NMR principle, the resonant energy between RF magnetic fields and atomic nuclear spins under static magnetic fields. The system was demonstrated as a RF biosensing platform in a personalized medicine setting (Sun et al., 2009, 2011).

[Fig. 9]

The T_2-relaxation time (or transverse relaxation time) as a sensing parameter of the RF biosensor is used. The reversal of T_2-relaxation time ($1/T_2$) exhibits linear characteristics with biotinylated MNP concentration. Finally, when avidin is bound to the MNPs, the T_2-relaxation time is shortened, as shown in Fig. 10, compared to that of biotinylated MNPs. From the measured results, the sensing platform is very useful for detection of small biomolecules in solution and the sensitivity and LOD (~20 fM level) is enhanced. However, the RF biosensor should be essentially used for labeling technique of MNPs-conjugated anti-biomolecules.

[Fig. 10]

3.2.2. Resonator-PCB system-based biosensor

An active system-based RF biosensor that combines a planar low-Q resonator has recently been developed at 2.4 GHz (Kim et al., 2013). The sensing system shown in Fig. 11 is a simple, low cost, and miniaturized sensing platform. The input impedance of a planar resonator with a biomolecular immobilization varies depending on the biomolecular concentration; consequently, the corresponding

change results in a frequency change in an oscillator. The sensitivity of the proposed system is enhanced by the use of a SAW filter with a very high-Q factor (~2000). The steep skirt characteristics of the SAW filter amplifies a small change in the oscillation frequency due to low biomolecular concentration to produce a large output signal at the detector.

[Fig. 11]

Fig. 12 shows the sensing parameters including oscillation frequency, output power of the SAW filter, and output voltage of the power detector at varying biomolecular concentrations. The biosensor produces a clear distinction between three different biomolecular concentrations (i.e., 100, 10, and 1 ng/ml). Moreover, the biosensor based on frequency shift can also reflect the differences in weight-mass of target biomolecules (i.e., streptavidin and cDNA). The minimum detectable limit of this RF biosensor is about 1 ng/ml. The sensing platform is cost-efficient, easy of fabrication. Moreover, rapid and real-time detection are possible. However, it should be still dried for sample measurement.

[Fig. 12]

4.3. NFMI system

DNA diagnostics based on NFMI for bioassay applications have also been investigated (Friedman et al., 2005). The NFMI system can achieve noncontact, label-free detection of low surface coverage analyte species with sensitivities comparable to conventional fluorescence bioassays. Figs. 13 (a) and (b) show the response and array layout used for hybridization, respectively. The NFMI images shown in Figs. 13 (c), (d), and (e) were scanned with 25 micron resolution in the x and y directions. The DNA images of three configurations are clearly differentiable. The use of a label-free technique with an NFMI system for enhancement the contrast between species of interest and other materials, such as water or salt residue, requires strict control over sample preparation and measurement. In future, this challenge can be partially resolved by in situ measurement in a buffered environment.

[Fig. 13]

[Table 4]

5. Conclusions and Future perspective

The development of RF biosensors for biomolecular detection is a very recent trend and is still in the early stages of defining and demonstrating the potentialities of the techniques. This review has presented the recent advances and research trends with respect to RF biosensors aimed at detection of various biomolecules including biotin-streptavidin, DNA hybridization, and glucose. To date, most RF sensing schemes for biomolecular recognition have been based on RF passive devices and circuits (e.g., various resonators and IDCs), as shown in Table 4. The simplest RF biosensors have been mostly focused on fundamental studies (such as extraction of electric components from an equivalent circuit, analysis of surface effects on electrode, mechanism of frequency shift, and Q-factor variation) for examining the interactions between RF and biomolecules. These studies have confirmed that combination of a passive circuit-based RF sensor with an active system, can markedly improve the performance of the sensor when compared to passive-only sensors. In addition, the output parameters of the active system-based RF biosensors could be easily measured with simple equipment. On the other hand, the NMR-based RF biosensor is able to detect biomolecules with magnetic nanoparticles; thus, this platform has potential applications in routine clinical analysis because it is possible to detect a target analyte in a solution. Another powerful sensing scheme is the recently described resonator-active system RF biosensor, which has revealed sufficient possibility as a cost-efficient biochip sensor module because the sensing part is separable from the active system. Of course, some limitations remain (e.g., low sensitivity (~ng/ml), dry bioprocesses, expensive equipment, etc.) before application to diverse biomedical and environmental sensing platforms can be achieved. Overcoming these problems will require combination of the RF biosensing schemes and disposable RF biochips with various materials and methods, such as the carbon nanomaterials and nanotechniques used in microfluidic systems, to

give rise to highly sensitive and direct detection. In particular, simple and user-friendly RF biochips need to be developed to allow cost-effective, miniaturized, and disposable POC diagnosis. Furthermore, the combination of an RF electrode with various nanomaterials would be extremely useful not only for detection of small biomolecules but also for the fabrication of biosensors for diagnosis of various cancers as well as food pathogens. Clearly, the realization of robust RF sensing platforms with high sensitivity, low detection limits, and label-free techniques for biomedical applications will require multidisciplinary research. We expect that the study of RF biosensors will open up new directions in research in the biomedical, environmental, and other high performance sensor fields.

Acknowledgements

This research has been supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0013194). (should be modified and added)

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Figure legends

Fig. 1. Schematic of a biosensor: a detector, a transducer, and a signal conditioner.

Fig. 2. Each type of typical RF biosensors.

Fig. 3. Measurement system for micro/nano-sized RF biosensors. The system consists of a VNA, a probe station, and a monitor.

Fig. 4. Bioprocess for RF biosensors. (a) Immobilization on the RF resonator: 1st step is immobilization of thiol-linked biotin (the upper image) and ssDNA (the lower image), 2nd step is BSA blocking to prevent non-specific binding, and 3rd step is binding of the specific analytes [i.e., streptavidin (the upper image) and cDNA (the lower image)]. (b) Immobilization on the CNT surface: 1st step is linker binding, 2nd step is immobilization of biotin, and 3rd step is binding of streptavidin. Reproduced from Kim et al. (2013) by permission of Elsevier Science Ltd., USA.

Fig. 5. Schematic of an asymmetric SRR-based RF biosensor. (a) The schematic of resonator based on a high-impedance microstrip line. (b) The geometric parameters of resonator (w=s=0.2 mm, lx=ly=1.68 mm, and δx=0.44 mm). (c) The current mode of the resonator by a time-varying magnetic field and (d) the image of a fabricated sample. Reproduced from Lee et al. (2013) by permission of AIP, USA.

Fig. 6. Frequency shift as the biological process for α-amylase detection. (a)-(e) are the frequency shifts to approximately 300, 200, 100, 10, and 1 unit/ml, respectively; (f) is the negative control. Reproduced from Lee et al. (2013) by permission of AIP, USA.

Fig. 7. Schematic of an IDC-CNT-based RF biosensor. (a) The schematic of the IDC based on a G-S-G electrode. (b) The gap between electrodes (SEM image). (c) The CNTs between electrodes (AFM image). Reproduced from Lee et al. (2008) by permission of KIEES, South Korea.

Fig. 8. Frequency and phase variation with biomolecular binding onto CNT. (a) Magnitude, (b) Phase of each configuration: 1st step-only IDCs without CNT, 2nd step-IDCs with CNT, 3rd step-biotinylated CNT, and 4th step-binding of streptavidin-biotin.

Fig. 9. System of a miniaturized NMR-system-based RF biosensor and principle of NMR. (a) The NMR-system-based RF biosensor consists of a magnet, a PCB circuit with silicon RF transceiver IC, and a planar micro-coil. (b) After transmitting RF energy in the spin alignment state, the relaxation time by spin-spin interaction is reduced by biomolecular binding. Reproduced from Sun et al. (2013) by permission of Elsevier Science Ltd., UK.

Fig. 10. T_2-relaxation time with biotinylated MNPs and avidin binding. (a) Variation in the T_2-parameters with MNP and avidin concentrations. (b) Inversion T_2-relaxation time versus magnetic nanoparticle concentration. (c) T_2-relaxation variation versus avidin concentration. Reproduced from Sun et al. (2009) by permission of IEEE, USA.

Fig. 11. Resonator-active system-based RF biosensor: (a) the overall schematic of the RF biosensor, (b) the layout of system with resonator (top view), (c) the circuit diagram of oscillator and buffer amplifier. Reproduced from Kim et al. (2013) by permission of Elsevier Science Ltd., USA.

Fig. 12. Frequency, amplitude, and voltage as the biomolecular immobilization: (a) oscillation frequency, (b) output power, and (c) power detector of the biotin-streptavidin binding system; (d) oscillation frequency deviation, (e) output power, and (f) power detector of the DNA hybridization system. Reproduced from Kim et al. (2013) by permission of Elsevier Science Ltd., USA.

Fig. 13. Near-field microwave measurements on DNA monolayers. (a) Response curve for DNA monolayers. Data scatter is dominated by uncertainty in DNA coverage, not by the NFMI measurement. (b) Array layout used for hybridization imaging experiments. (c) An as prepared array. The NFMI image confirms the layout of immobilized P1 and P2 sequences. (d) After hybridization to a sequence complementary to P1. (e) After array regeneration and hybridization to a sequence complementary to P2. The hybridized images in panels (d) and (e) are difference images obtained after subtraction of the unhybridized image in panel (c). Reproduced from Friedman et al. (2005) by permission of American Chemical Society, USA.

Table legends

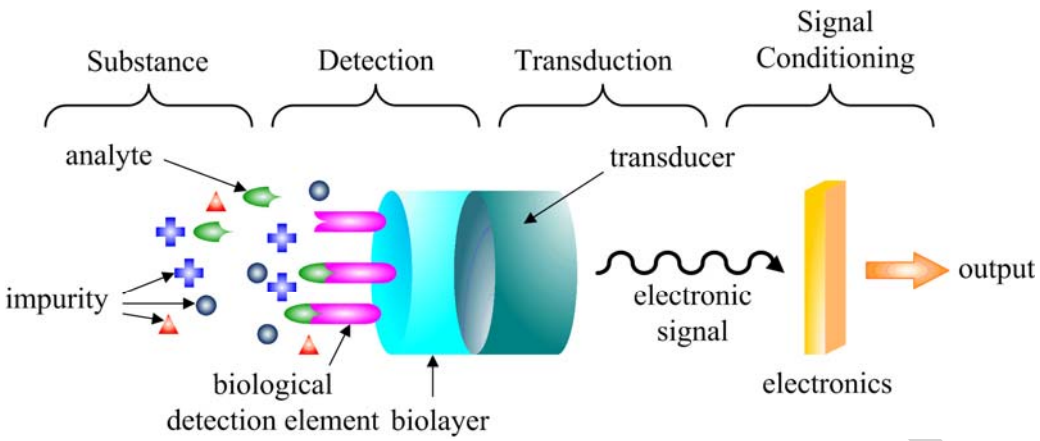
Table 1. Representative RF biosensors as working principle, sensing parameter, operating frequency and target molecules.

Table 2. Various RF biosensor types are listed along with their target biomolecules, detection method and limit.

Table 3. Surface modification of detector types and target biomolecules.

Table 4. Summary of recently developed RF biosensor types.

Fig. 1



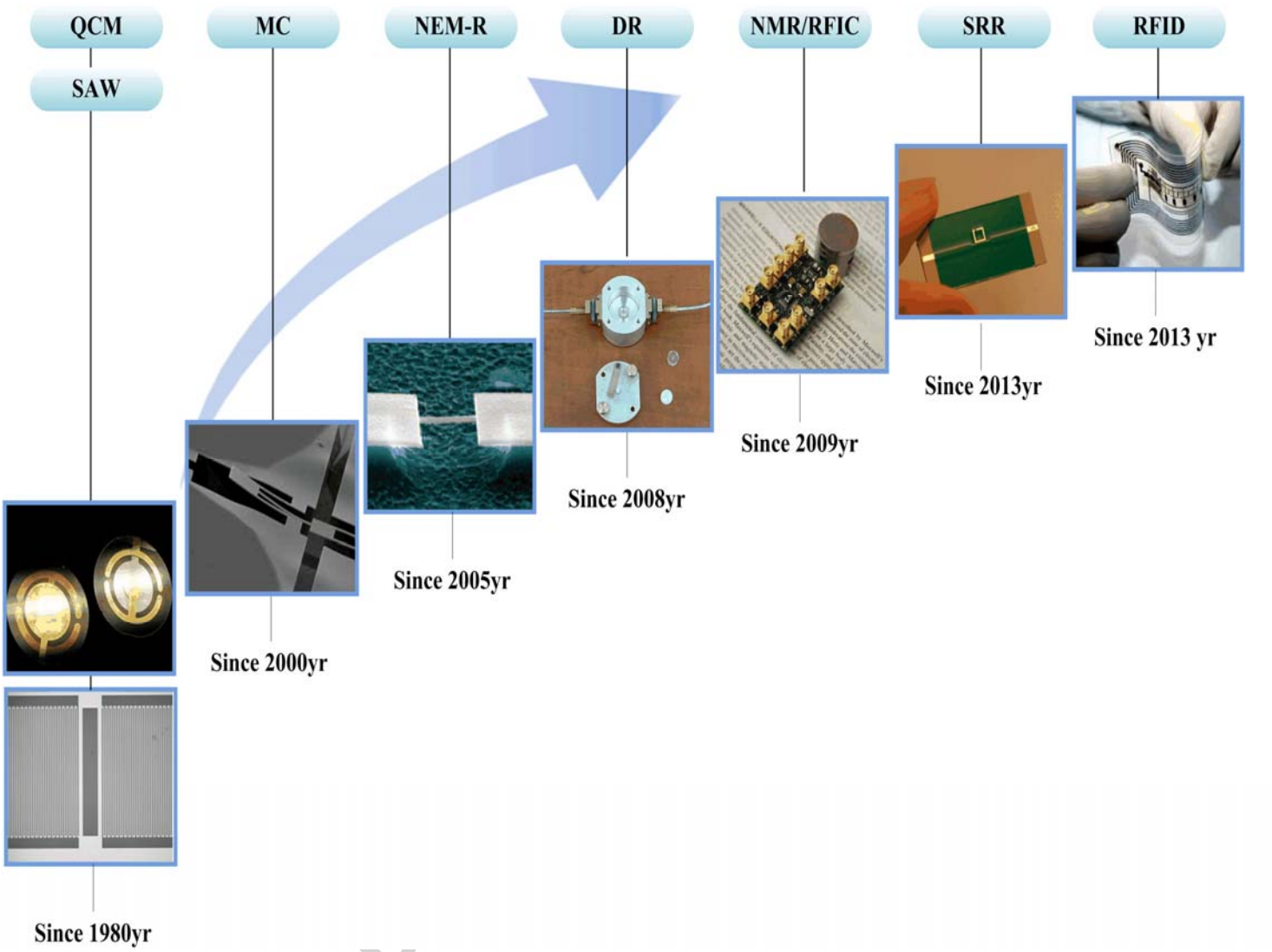

QCM
SAW
MC
NEM-R
DR
NMR/RFIC
SRR
RFID
Since 1980yr
Since 2000yr
Since 2005yr
Since 2008yr
Since 2009yr
Since 2013yr
Since 2013 yr

Fig. 2

Fig.3

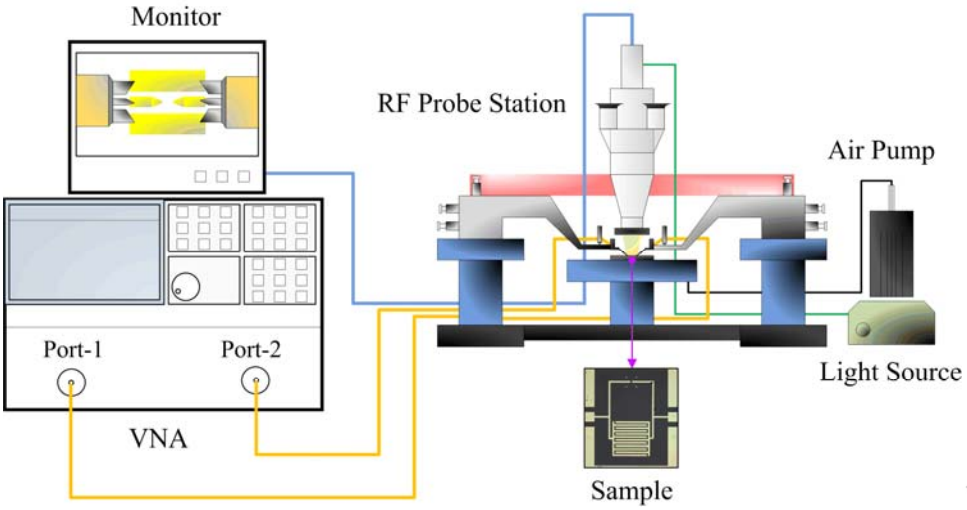

Monitor
RF Probe Station
Air Pump
Port-1
Port-2
VNA
Light Source
Sample

Fig. 4

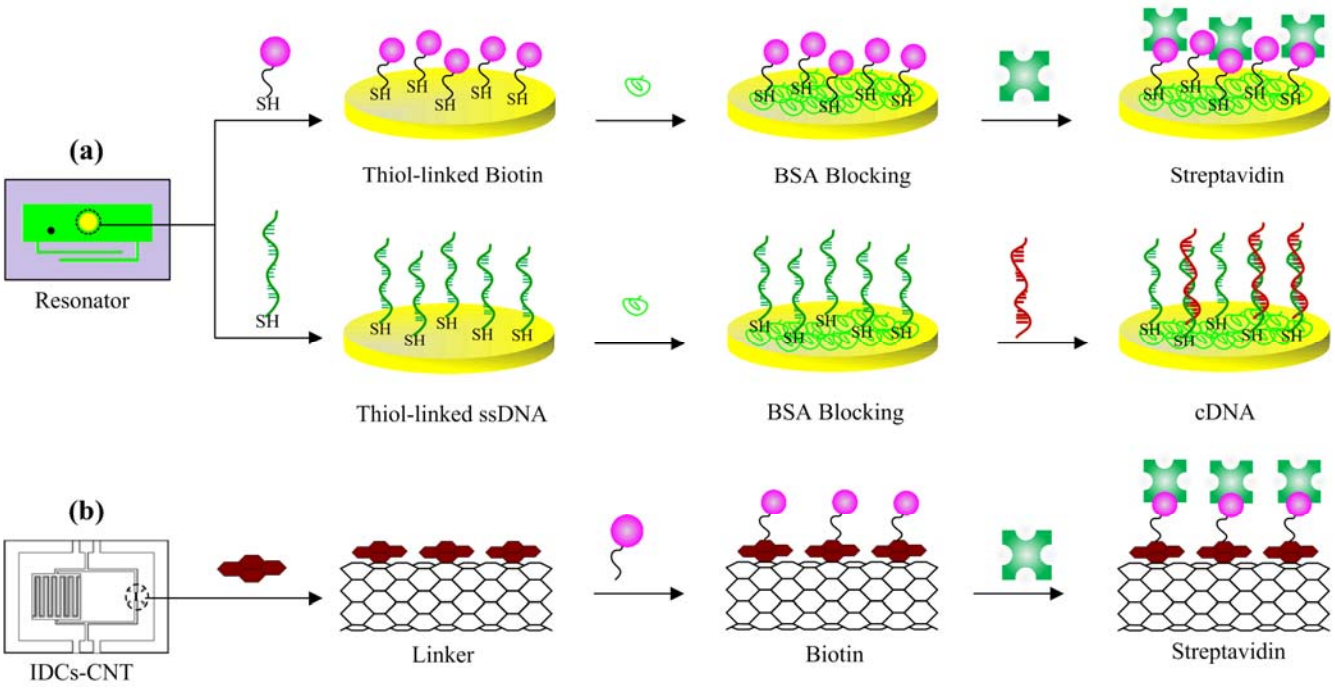

(a)
Resonator
SH
Thiol-linked Biotin
BSA Blocking
Streptavidin
Thiol-linked ssDNA
BSA Blocking
cDNA
(b)
IDCs-CNT
Linker
Biotin
Streptavidin

Fig. 5

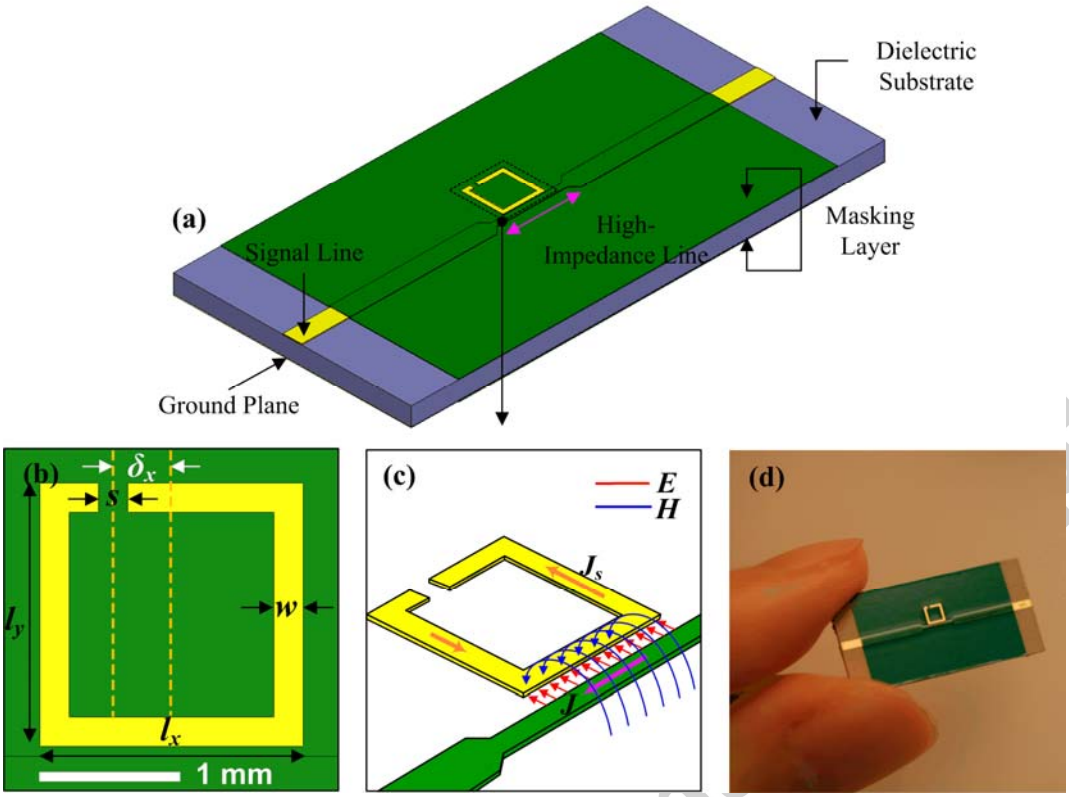


Fig. 6

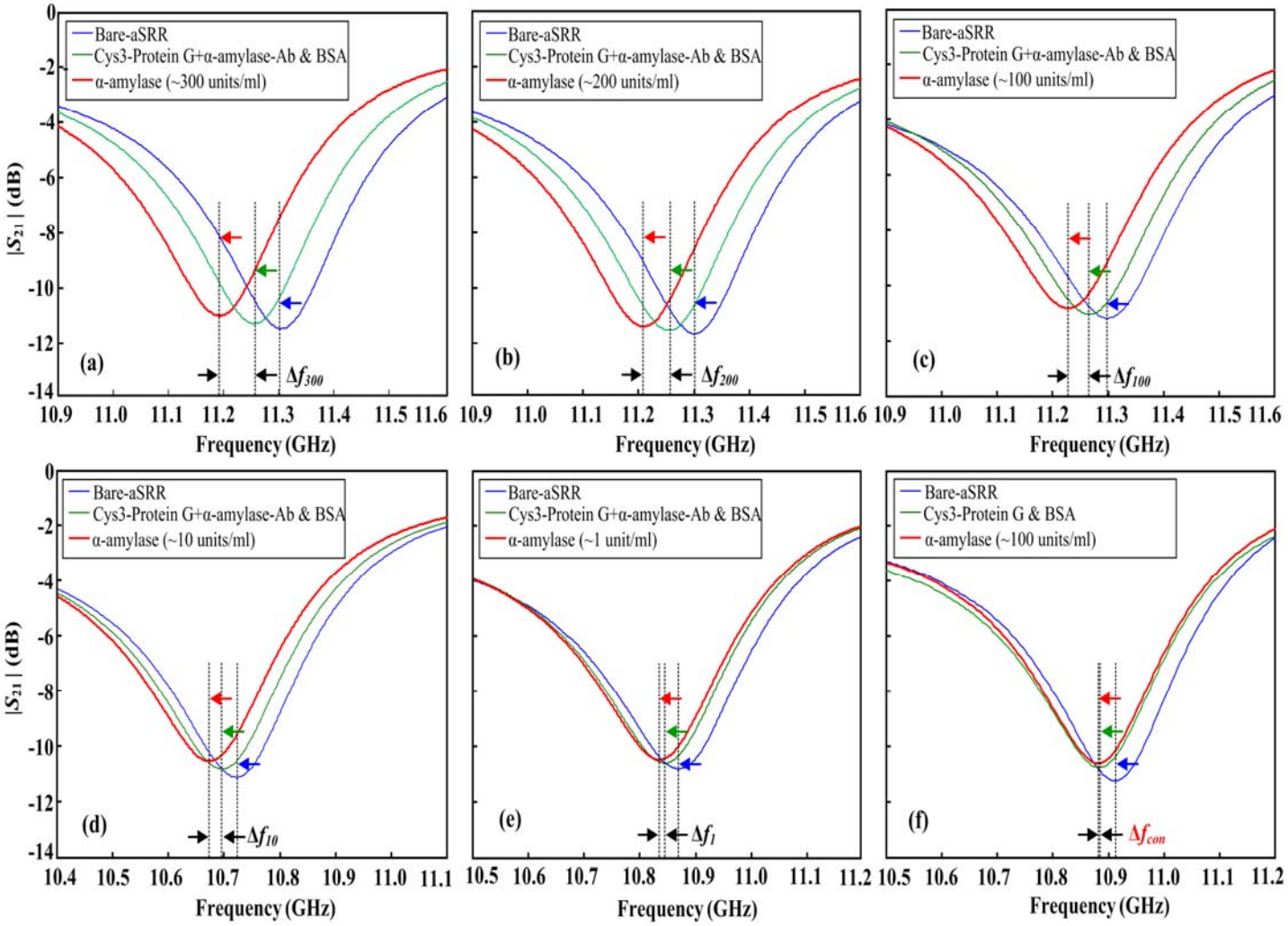

Bare-aSRR
Cys3-Protein G+α-amylase-Ab & BSA
α-amylase (~300 units/ml)
(a)
Δf300
α-amylase (~200 units/ml)
(b)
Δf200
α-amylase (~100 units/ml)
(c)
Δf100
α-amylase (~10 units/ml)
(d)
Δf10
α-amylase (~1 unit/ml)
(e)
Δf1
Cys3-Protein G & BSA
α-amylase (~100 units/ml)
(f)
Δfcon
|S21| (dB)
Frequency (GHz)

Fig. 7

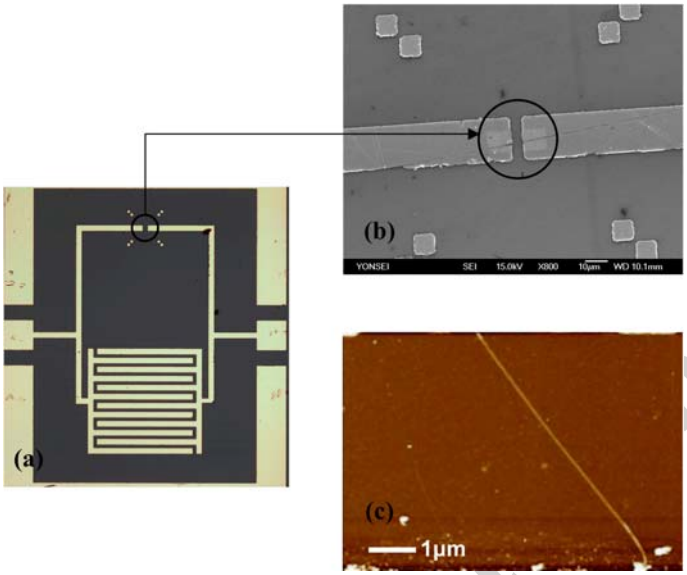


Fig. 8

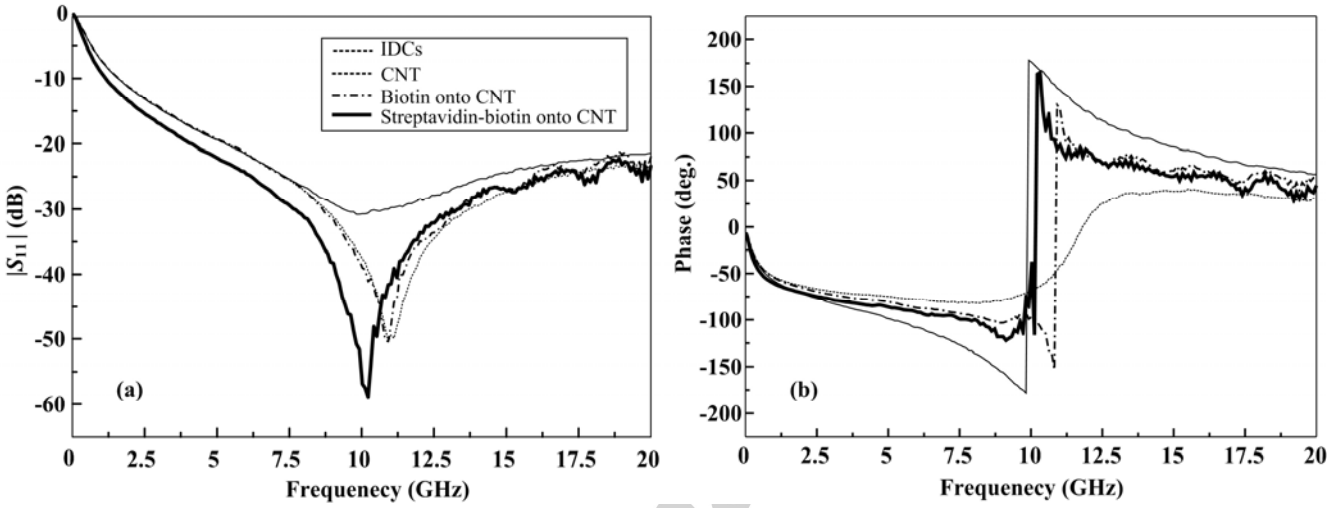


Fig. 9

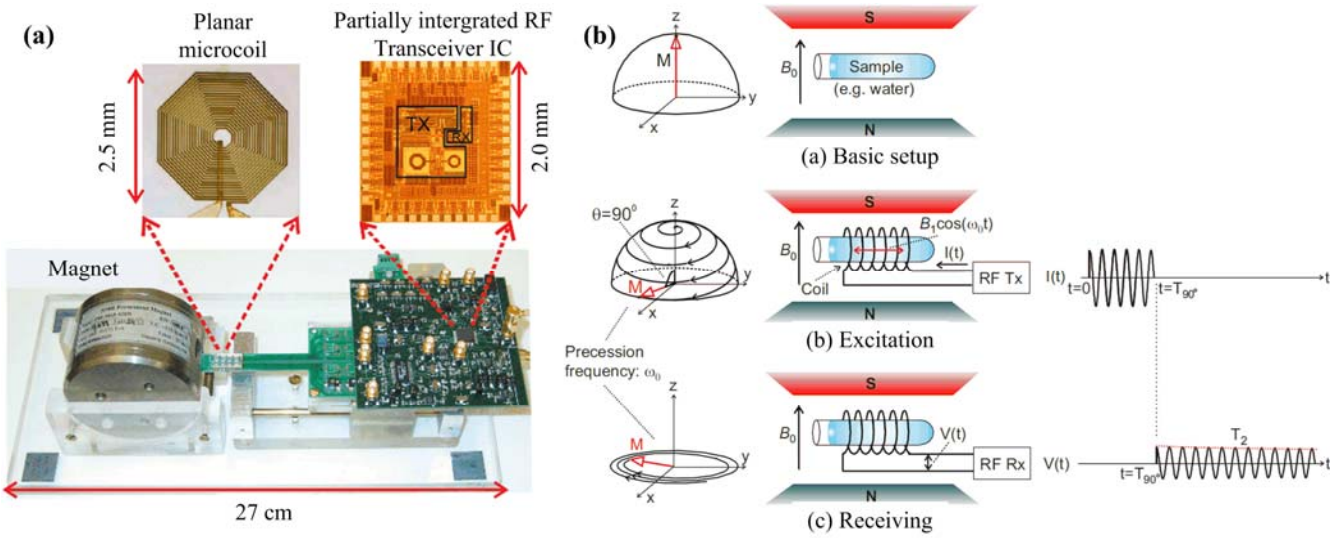
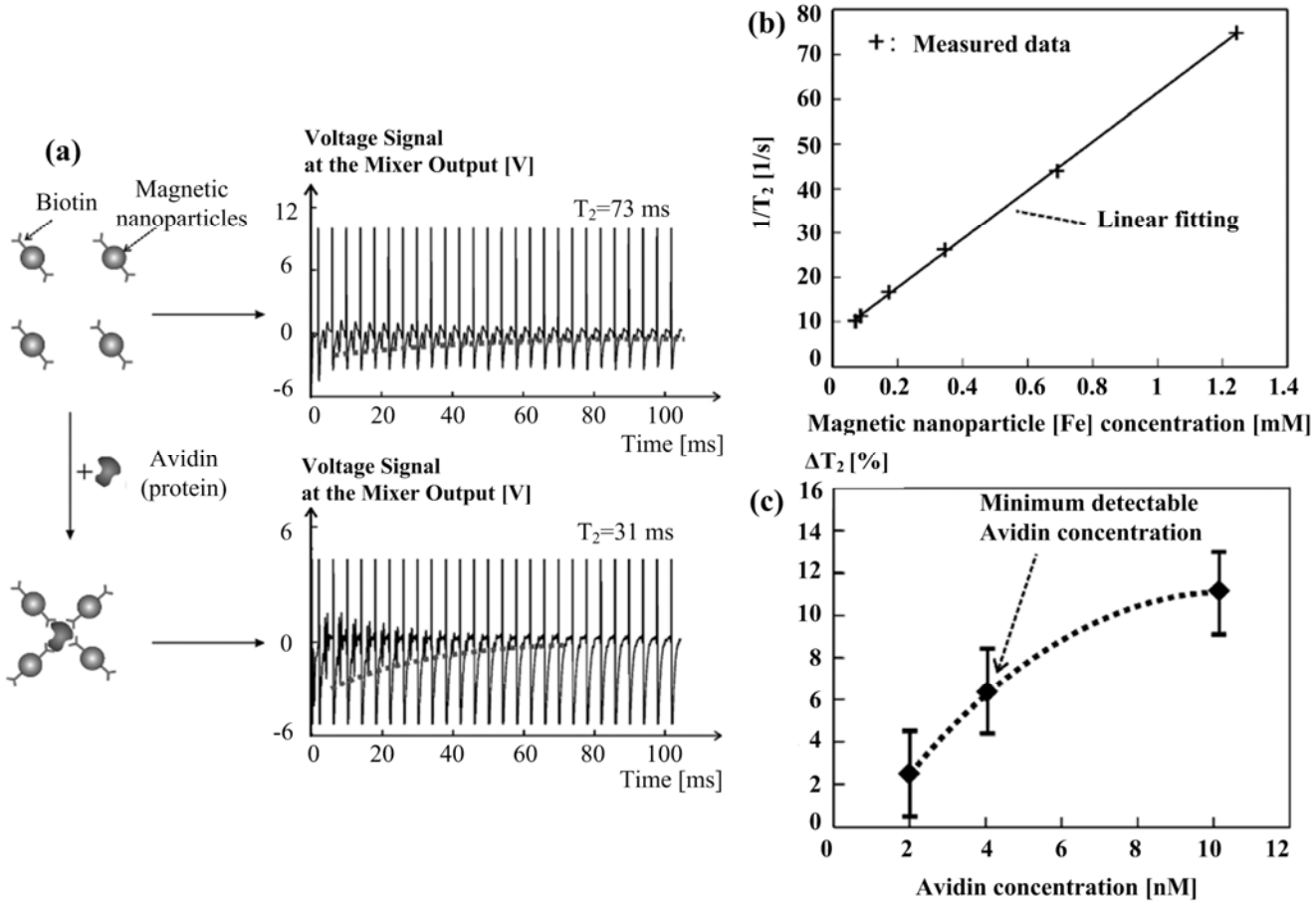


Fig. 10



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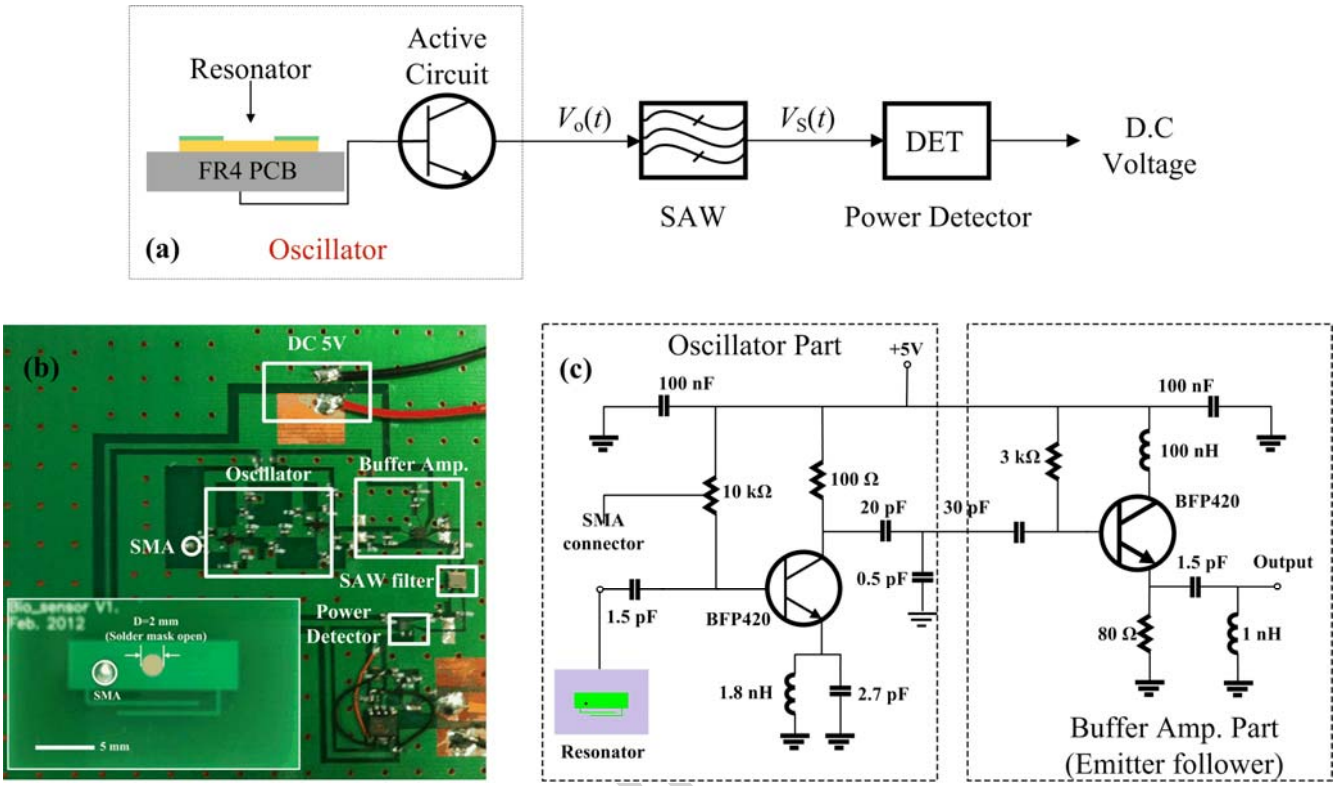

Fig. 12

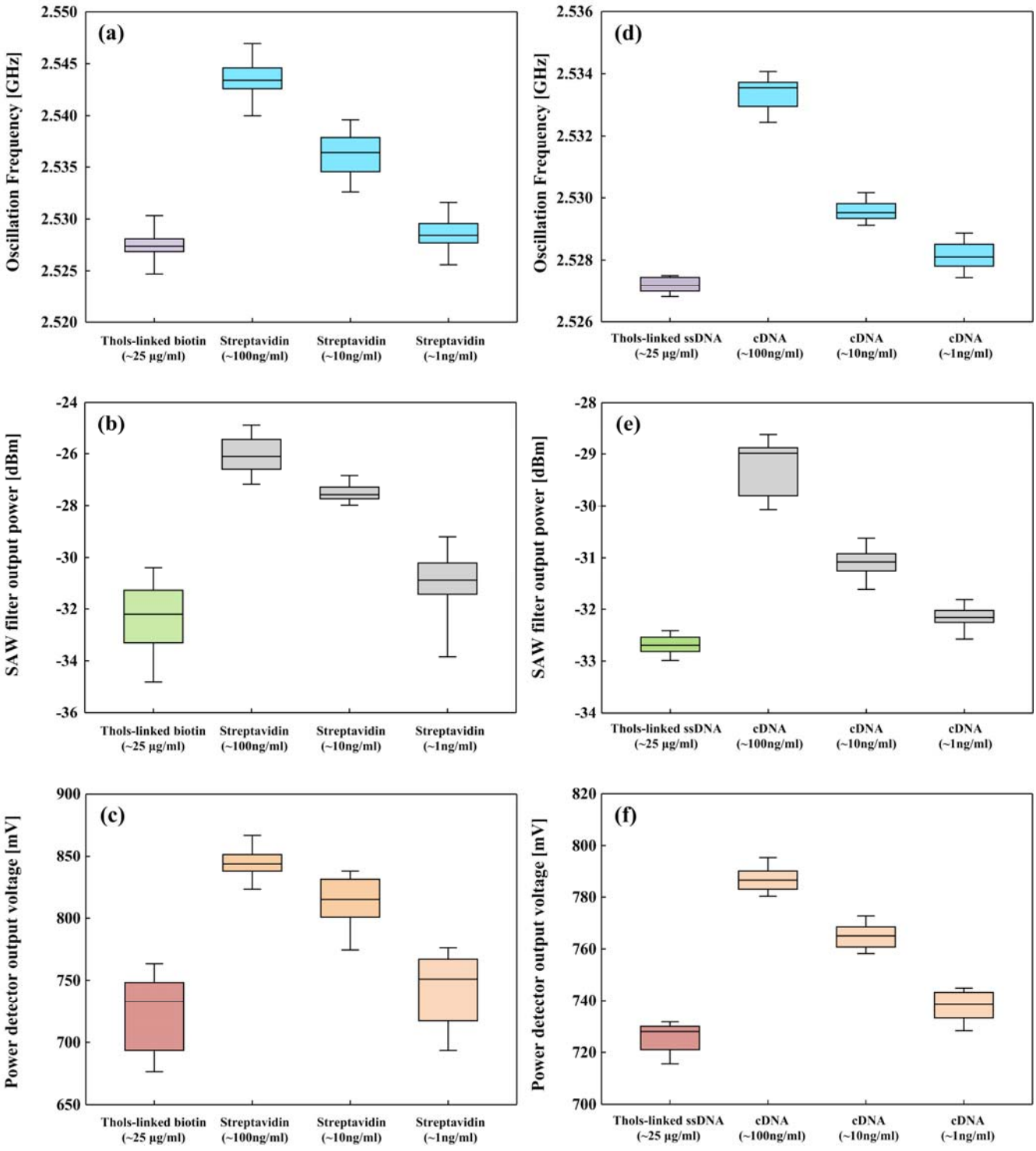
(a)
Oscillation Frequency [GHz]
2.550
2.545
2.540
2.535
2.530
2.525
2.520
Thols-linked biotin (~25 μg/ml)
Streptavidin (~100ng/ml)
Streptavidin (~10ng/ml)
Streptavidin (~1ng/ml)
(d)
Oscillation Frequency [GHz]
2.536
2.534
2.532
2.530
2.528
2.526
Thols-linked ssDNA (~25 μg/ml)
cDNA (~100ng/ml)
cDNA (~10ng/ml)
cDNA (~1ng/ml)
(b)
SAW filter output power [dBm]
-24
-26
-28
-30
-32
-34
-36
Thols-linked biotin (~25 μg/ml)
Streptavidin (~100ng/ml)
Streptavidin (~10ng/ml)
Streptavidin (~1ng/ml)
(e)
SAW filter output power [dBm]
-28
-29
-30
-31
-32
-33
-34
Thols-linked ssDNA (~25 μg/ml)
cDNA (~100ng/ml)
cDNA (~10ng/ml)
cDNA (~1ng/ml)
(c)
Power detector output voltage [mV]
900
850
800
750
700
650
Thols-linked biotin (~25 μg/ml)
Streptavidin (~100ng/ml)
Streptavidin (~10ng/ml)
Streptavidin (~1ng/ml)
(f)
Power detector output voltage [mV]
820
800
780
760
740
720
700
Thols-linked ssDNA (~25 μg/ml)
cDNA (~100ng/ml)
cDNA (~10ng/ml)
cDNA (~1ng/ml)

Fig. 13

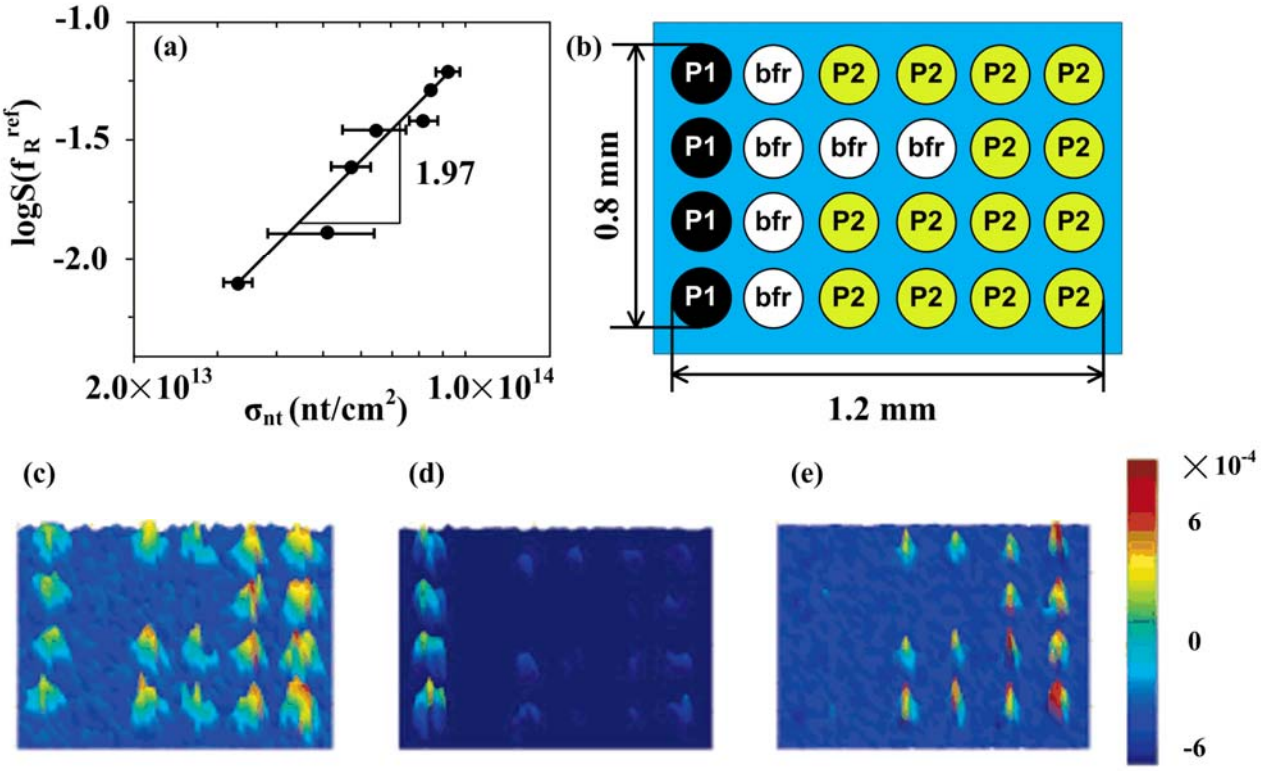

Table 1.

Category as working principle	Sensing parameter	Operating frequency	Target molecules	Reference
Piezoelectric resonance				
SAW	Frequency shift	~10 MHz	IgG	Roederer et al. (1983)
QCM	Frequency shift	~9 MHz	cDNA	Caruso et al. (1997)
MC	Frequency shift	~30-140 kHz	IgG	Moulin et al. (2000)
NanoMR	Frequency shift	~11-12 MHz	dsDNA	Ilic et al. (2005)
Electromagnetic resonance				
DR	Frequency shift	~4.5 GHz	Glucose	Lee et al. (2008)
SRR	Frequency shift	~10-12 GHz	α-amylase, cortisol	Lee et al. (2013)
NMR				
NMR-RFIC	T1 and T2 relaxation time	~21MHz	Biotin-streptavidin	Sun et al. (2009)
Antenna				
Dipole antenna-RFID	Detection length of antenna	~915 MHz	IgG	Yuan et al. (2013)

Table 2.

Schemes of biosensors	Target biomolecules	Detection method	Detection limit	References
Passive devices and circuits				
Nanogap-IDCs	RNA-aptamer	Label free	-	Lohndorf et al. (2005)
LC resonator	GOx, PDAS	Label free	-	Kim et al. (2006)
	Biotinylated BSA	Label free	0.01 nM	Caglayan et al. (2010)
Slotline ring resonator	Biotin-streptavidin	Label free	-	Kim et al. (2008)
Double SRR array	Biotin-streptavidin	Label free	-	Lee et al. (2008)
Dielectric resonator	Glucose, Hg	Label free	-	Kim et al. (2009), Basey-Fisher et al. (2013)
IDCs	CRP	Label free	5 ng/ml	Saravan et al. (2008)
CPW	IgG	Label free	-	Chen et al. (2009)
Double SRR	Cortisol-BSA	Label free	100 pg/ml	Lee et al. (2011)
Symmetric/asymmetric SRR	PSA, cortisol, α-amylase	Label free	1 ng/ml	Lee et al. (2012, 2013)
Microwave cavity	Pig-blood D-glucose	Label free	150 mg/dl	Kim et al. (2012)
Polymer-transmission layer	DNA hybridization	Label	10 pM	Yang et al. (2012)
Passive devices and circuits-nanomaterials				
IDCs-gold nanoparticle	RIgG-GaRIgG	Label	1 ng/μl	Chien et al. (2007)
IDCs-carbon	Biotin-streptavidin	Label free	100 nM	Lee et al.

nanotube				(2008)
IDCs-graphene oxide	Biotin-streptavidin	Label free	-	Yoon et al. (2013)
	glucose	Label free	1 mM	Park et al. (2014)
RFID-gold nanoparticle	IgG	Label	20 ng/ml	Yuan et al. (2013)
Active devices and circuits-system				
NMR-RFIC system	Biotin-streptavidin	Label	20 fM	Sun et al. (2009)
Resonator-PCB system	DNA hybridization, Biotin-streptavidin	Label free	1ng/ml	Kim et al. (2012, 2013)
NFMI-system	DNA	Label free	6 molecules/μm^2	Friedman et al. (2005)

Table 3.

Detector types	Surface modifications	Target biomolecules	References
Au	Thiols-linked biotin	Streptavidin	Kim et al. (2012, 2013)
	Thiols-lined ss-DNA	c-DNA	Kim et al. (2012, 2013)
	Cystein3-linked protein G Anti-PSA	PSA	Lee et al. (2012, 2013)
	Cystein3-linked protein-G Anti-α-amylase	α-amylase	
	Glucose oxidase	Glucose	Park et al. (2014)
CNT	1-pyrenebutanoic acid succinimidyl ester-Biotin	Streptavidin	Lee et al. (2008)
GO	Glucose oxidase	Glucose	Yoon et al. (2013)

Table 4.

Category of biosensors	Advantages	Disadvantages	References
Passive devices and circuits			
SRR	Label free detection Rapid detection Simple and small structure Low cost Small specimen	Dried sample Simple fabrication Bulky measurement system	Lee et al. (2008, 2010, 2011, 2012, 2013)
Passive devices and circuits-nanomaterials			
IDCs-CNT/GO	Label free detection Rapid detection Simple and small structure Enhanced sensitivity Small specimen	Complex functionalization Complex fabrication Dried sample Bulky measurement system	Lee et al., (2008, 2011), Yoon et al. (2013)
Active devices and circuits-system			
NMR-RFIC system	Rapid detection Low cost and miniaturized platform Detection in solution	Label detection Simple measurement system	Sun et al. (2009, 2011)
Resonator-PCB system	Label free detection Low cost and miniaturized platform Real-time detection Small specimen	Dried sample Simple measurement system	Kim et al. (2012, 2013)
NFMI system	Label free detection Noncontact detection Low surface coverage analyte	Dried sample Non in-situ measurement	Lee et al. (2005)