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Contact-Free, Passive, Electromagnetic Resonant Sensors for Enclosed Biomedical Applications: A Perspective on Opportunities and Challenges

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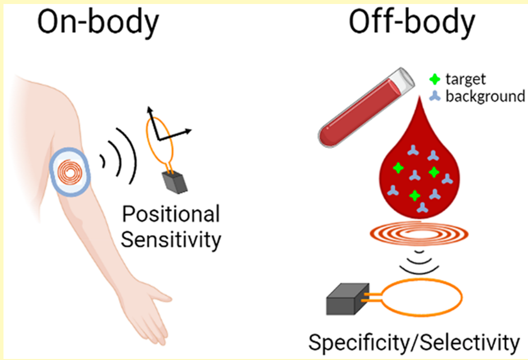
ABSTRACT: Inexpensive and accurate tools for monitoring conditions in enclosed environments (through garments, bandages, tissue, etc.) have been a long-standing goal of medicine. Passive resonant sensors are a promising solution for such wearable health sensors as well as off-body diagnostics. They are simple circuits with inherent inductance and capacitance (LC tank) that have a measurable resonant frequency. Changes in local parameters, e.g., permittivity or geometry, effect inductance and capacitance which cause a resonant frequency shift response. This signal transduction has been applied to several biomedical applications such as intracranial pressure, hemodynamics, epidermal hydration, etc. Despite these many promising applications presented in the literature, resonant sensors still do not see widespread adoption in biomedical applications, especially as wearable or embedded sensing devices. This perspective highlights some of the current challenges facing LC resonant sensors in biomedical applications, such as positional sensitivity, and potential strategies that have been developed to overcome them. An outlook on adoption in medicine and health monitoring is presented, and a perspective is given on next steps for research in this field.



KEYWORDS: *chipless RFID, wireless sensors, LC resonators, resonant sensors, wearable sensors*

A unique design constraint for biomedical sensors is the need to transduce information through enclosed and or opaque materials such as skin or bandages. Contact approaches, such as wired electrodes or sampling via natural or engineered fistulas (e.g., Alexis St. Martin's famous gunshot hole giving access to his gastric system[1]) are nonideal for living systems due to complications of inflammation and infection; thus contact-free approaches remain a pursuit of modern research. Such approaches can be organized into three categories based on modes of delivering energy: (1) powered, (2) semiactive, and (3) passive. Passive systems refer to sensing modalities that do not require on-board batteries or rectified wireless power transmission to power the sensor. Instead, they use electromagnetic radiation to both excite the sensor directly and receive feedback from the sensor. Although these sensors are more limited in read range, the distinct advantages of simplicity and low cost make them compelling for many sensing problems in enclosed, opaque systems.

The simplest way to classify passive sensors for opaque, enclosed systems is according to the spectra of electromagnetic radiation (EMR) that interact with the sensors. EMR interactions with matter cannot be adequately discussed in depth here (see these texts in refs 2 and 3); for the sake of this perspective we simplify EMR−matter interactions broadly to absorbance, scattering, and transmittance. Absorbance is when the EMR photon energy is accepted by an electron transition state of the material; scattering is when the photon trajectory is altered; transmittance occurs when the photon passes through the material unhindered. For enclosed biological applications, we will limit the interacting matter of interest to low atomic mass elements that are highly prevalent in biomedical applications such as hydrogen, carbon, oxygen, and nitrogen.

The electromagnetic spectrum exhibits four EMR windows to biological materials. These are readily observed in the absorption spectra of water (Figure 1), which has similar windows in plastics and other biomaterials (proteins, sugars, and fats). From highest frequency (or energy) to lowest, these windows of low absorption are (1) γ rays (300−30 EHz), (2) hard X-ray (3−30 EHz), (3) near-infrared (100−300 THz), and (4) high-frequency radio waves (1−100 MHz). γ-rays and

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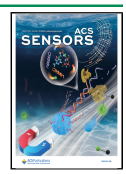

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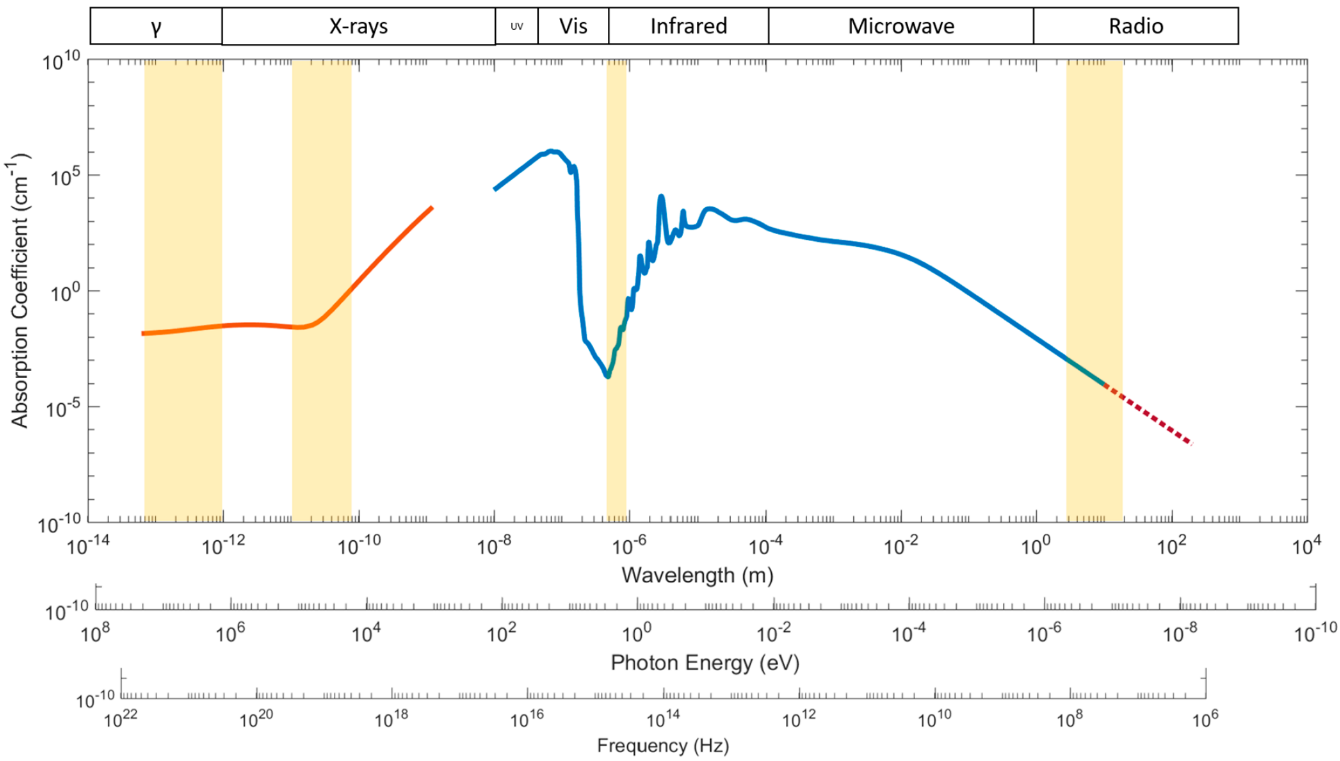

Figure 1. Absorption of electromagnetic radiation (EMR) in water showing the four "transparent" windows for EMR communication to passive, wireless sensors for biomedical applications: γ rays, hard X-rays, near-infrared, and high-frequency radio waves. Top boxes of the plot show the EMR regions. Axes are included for wavelength, photon energy, and frequency. Data shown are compiled from three sources: X-ray absorption (red) from NIST,[6] UV to microwave (blue) from Segelstein,[7] and radio (dashed line) from an empirical model.[8]

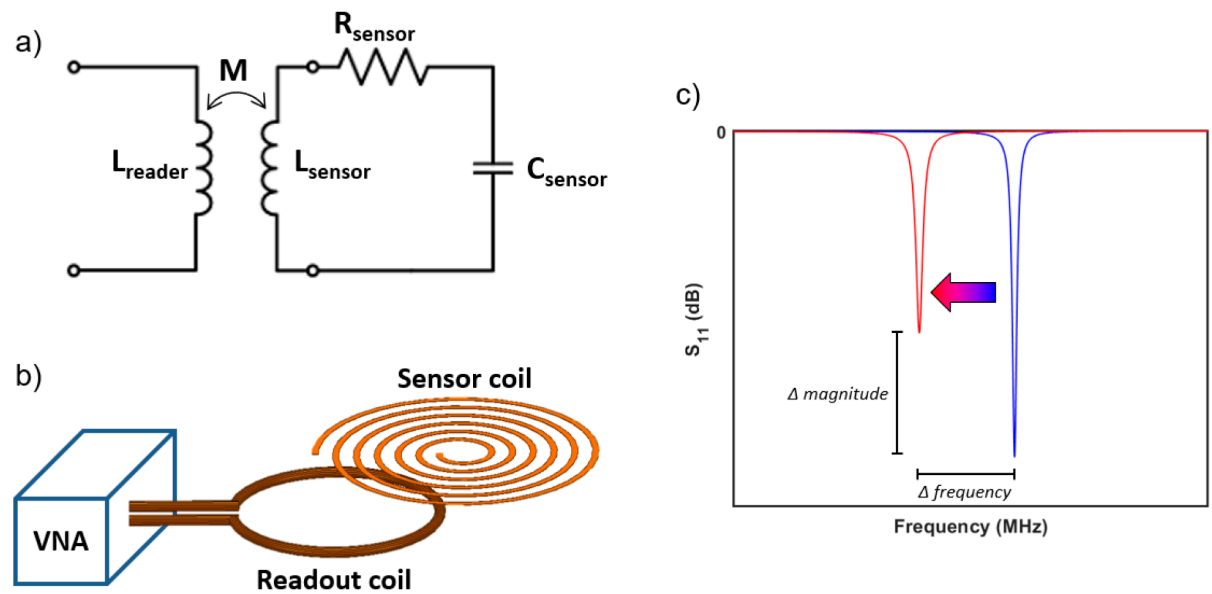

Figure 2. Wireless, passive resonant sensor system. (a) Equivalent circuit of the sensor system. (b) Schematic of the sensor system. (c) Signal response curve obtained through VNA.

X-rays exhibit near 100% transmittance due to energetic (10–10,000 keV) photons that are higher in energy than electronic transitions permitted in low valence electron atoms. At the near-infrared "tissue-transparent" window (at 650–1350 nm), EMR experiences relatively low absorption in water, blood, and tissue proteins.[4] However, significant scattering and autofluorescence increase the background signal and limit system penetration depth.[5] At radio frequencies below 100 MHz, photon energy is too small to couple with the electron transition levels, and absorption is again small. Wavelengths at the 100 MHz frequency (3 m) become sufficiently large that a large amount of material is required to "see" the EMR (e.g., a human body, or small medical device is too thin to interact). Below 1 MHz, the penetration depth continues to improve

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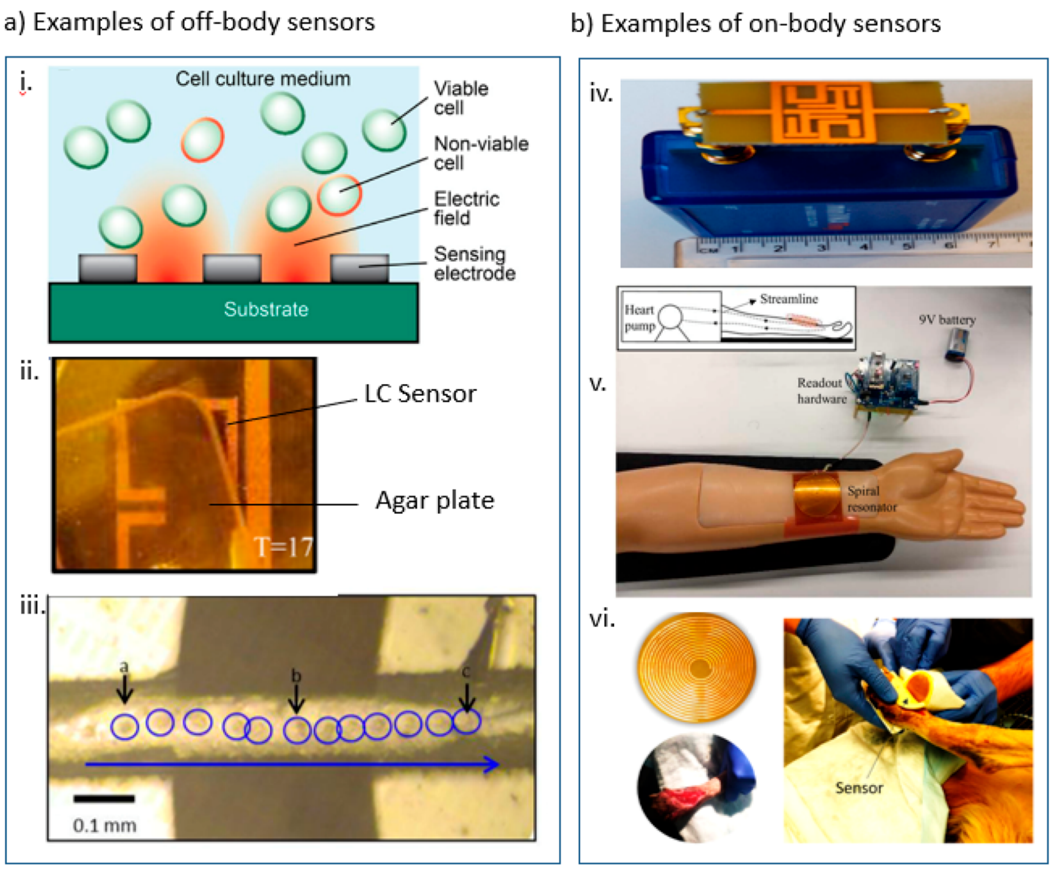

Figure 3. Examples of resonant sensors for biomedical applications in literature. (a) Off-body sensors: (i) extended split ring LC resonator for monitoring growth of bacteria on solid media with sensor response (Reprinted with permission from ref 31. Copyright 2021 IEEE); (ii) capacitive sensing of viable/nonviable cells with frequency response for classification (Reprinted with permission from ref 32. Copyright 2019 Elsevier), and (iii) LC resonant sensor response of alternating buffer and cells through microfluidic channel (Reprinted with permission from ref 33. Copyright 2020 IEEE). (b) On-body sensors: (iv) muscle tissue analysis bandstop LC resonant sensor (Reprinted with permission from ref 34. Copyright 2021 MDPI), (v) LC resonant sensor for monitoring hemodynamics in arm (Reprinted with permission from ref 16. Copyright 2019 IEEE), (vi) embedded resonant sensor in bandage for wound monitoring (Reprinted with permission from ref 35. Copyright 2021 American Chemical Society).

(e.g., submarine communications in the window of 3−30 kHz); however, as wavelengths increase, the size requirements of transmitters and receivers become impractically large (wavelength is 100 m at 1 MHz) for medical sensors. This perspective will focus on the unique benefits and limitations of short-wave RF resonant sensors.

Passive RF resonators meet critical criteria for biomedical sensors while simultaneously meeting needs of simplicity and cost. First, they have a fast response, operating at radio microwave frequencies and responding to changes in dielectric properties of a substrate as quickly as the frequency has time to polarize a substrate (nanoseconds[9,10]). Second, they are structurally robust, with many applications in harsh environments[11−13] and maintaining their frequency response even after being partially damaged.[14] Third, the sensors are demonstrated to be non-invasive/minimally invasive and have been used to monitor inside closed systems through nonmetallic materials including human skin.[15−19] Finally, their readout method is simple, requiring lower cost components (no high-energy source like γ- or X-ray probes and no optical setups such as those required for near-infrared sensors), and more readily applicable to portable readout. Resonant sensors have been applied to many physical systems over the past six decades, and many excellent reviews are present in the literature.[20−23] This perspective does not seek to reiterate these; instead, it focuses on recent applications specifically in biomedical sensing and critically assesses their limitations that must be overcome to realize the long-held promise of inexpensive, contact-free monitoring in biomedicine.

This perspective is divided into four sections. First, a primer on the working mechanism of passive resonant RF sensors is given as background. Second, a brief literature review of recent examples of resonant sensors in biomedical applications is presented. Third, a critical assessment of strengths and weaknesses for this class of sensors is provided. Finally, an outlook is provided on future use and impactful research topics for these sensors in biomedical applications.

RESONANT SENSOR THEORY AND BACKGROUND

A passive, wireless LC sensor system is composed of a sensor circuit, a readout coil, and a signal measuring unit. The measuring unit electromagnetically couples to the sensor circuit which consists of resistive (R), inductive (L), and capacitive (C) components (Figure 2). When excited by the measuring unit, electrons oscillate between the capacitive and inductive elements. There is a frequency at which this oscillation is most efficient where the excitation frequency matches that inherent in the sensor circuit; this is termed the

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resonant frequency. The LC circuit is rendered into a sensor by engineering the design such that a target of interest creates a change in any of the LCR components; this causes a change in the reflection and transmission power and/or the resonant frequency. Reflection and transmission magnitudes are typically measured as scattering parameters of S_{11} and S_{21} respectively. However, for a wireless system, S_{11} and S_{21} magnitudes are inherently coupled with the interrogation distance, which limits the use case of this parameter. Conversely, the resonant frequency is dominated by the inductive and capacitive components. Most targets of interest do not vary in their magnetic properties (affecting inductance); thus, most resonant sensors are capacitive based.

With regard to the design of these sensors, the inductive component is usually a spiral or split ring which can inductively couple with the readout coil. The capacitive component can be self-capacitance of the spiral inductor (parasitic capacitance) or a secondary circuit that connects in parallel to the inductor, such as an interdigitated capacitor or a parallel plate capacitor. The ultimate choice of design is optimized according to the application; for instance, maximizing the sensitivity based on tuning the size of the electromagnetic fields created around the sensor. This optimization can be done in silico using finite element software packages such as Ansys Electronic Desktop HFSS or CST and solving for the governing Maxwell's equations.[24,25] The coupling reader coils are typically circular or rectangular loops sized to couple with the resonant sensor (represented by an inductor in the circuit diagram (Figure 2)). The signal measuring unit is a device that measures the impedance or reflection properties across a frequency range such as a vector network analyzer (VNA). Traditional rack VNAs for microwave circuit design have a high cost that would exclude resonant sensors from several applications; however, low-cost VNA options have been demonstrated[26−29] as well as lower cost, custom, portable readers[30] for sensing applications.

RESONANT SENSORS IN BIOMEDICAL APPLICATIONS

For the purposes of this perspective, resonant sensors will be discussed in terms of two different groups: off-body diagnostic devices and wearable or implantable sensors. This distinction is made to group sensors that can be operated in controlled environments (off-body diagnostics), such as detection of pathogenic bacteria in a biological sample, see Figure 3a, versus those that operate in variable conditions (wearable/implantable sensors), see Figure 3b. As will be discussed in the next section, there are certain design considerations that must be accounted for in both groups of sensors, but there are additional factors that must be considered for sensors that operate in a changing environment to maintain a robust sensor response, such as positional effects. A non-exhaustive list of resonant sensors employed in biomedical applications is given in Table 1 at the end of this section.

RESONANT SENSORS FOR OFF-BODY DIAGNOSTICS

Resonant sensors are sensitive to environmental conditions such as temperature and humidity, which influence the relative permittivity of the materials and, thereby, the sensor response. These environmental conditions can be controlled in a laboratory environment, where diagnostic samples are sent for testing. Cells, tissue, blood, saliva, and urine are common samples used for diagnostic analysis. The LC resonant sensors provide a diagnosis approach based on the variation in permittivity or other electrical properties, e.g., conductivity, in the tested samples. Some studies demonstrating these sensors as a diagnostic approach are discussed below. Unlike other diagnostic approaches that involve analyte binding (ELISA, SPR, BLI), these sensors have a fast response time and relatively lower capital and consumable cost.

Table 1. Examples of Resonant Sensors with Biomedical Sensing Applications

Application/Analyte	Sensor Modality	Refs
Enzyme activity	Off-body	40, 41
Viral RNA	Off-body	42
Low vol of samples	Off-body	43−46
Pathogenic bacteria	Off-body	47−51
Temperature	On-body	52,53
Live/dead cells	Off-body	32, 33, 54
Glucose	Off-body	17, 55−58
Glucose	On-body	59−66
Sweat volume/pH	On-body	29, 67
Intraocular pressure	On-body	37, 68−71
Edema	On-body	72, 73
Skin hydration/strain	On-body	74, 75
Wound monitoring	On-body	39, 76
Oral cavity	On-body	39

As off-body diagnostic sensors can be monitored under controlled conditions, they can measure either the magnitude of scattering parameters or the resonant frequency. For example the growth of bacteria on solid agar was monitored with an extended gap split ring resonator using the S_{11} reflection parameter with a sensitivity of 0.005 dB/h for bacterial growth.[31] Despite the relatively low sensitivity, noise was minimized by increased sensitivity from the extended gap creating a concentrated electric field in the sensing region. A more sensitive device that utilizes the magnitudes of the scattering parameters counts cells flowing through a microfluidic chip.[33] Proximity of a single cell across the resonator leads to an increase in magnitude of the S_{21} scattering parameter, allowing for a simple single cell counter. Cell viability has been found to be a function of both resonant frequency and scattering parameter magnitude with resonant sensors.[32] However, most biomedical applications of off-body resonant sensors analyze the resonant frequency of the device, such as a temperature sensing device with cascaded spiral resonant sensor.[36]

RESONANT SENSORS FOR WEARABLE HEALTH

Resonant sensors have also found utility as wearable devices starting with the seminal paper of an intraocular pressure sensor over 60 years ago.[37] Although wearable resonant sensors have been developed in laboratories for decades, they have seen little translation into clinical or consumer health practice. Some reasons for this include the fast development of microchips and processors that have developed chip-based wearable sensors that consume little power or are part of a device that is easily integrated into a telehealth environment, i.e., the emergence of IOT for personal health monitoring.[38] These advances have overcome many of the advantages of using resonant sensors (passive, lightweight devices). However, there are still some benefits of further development of resonant

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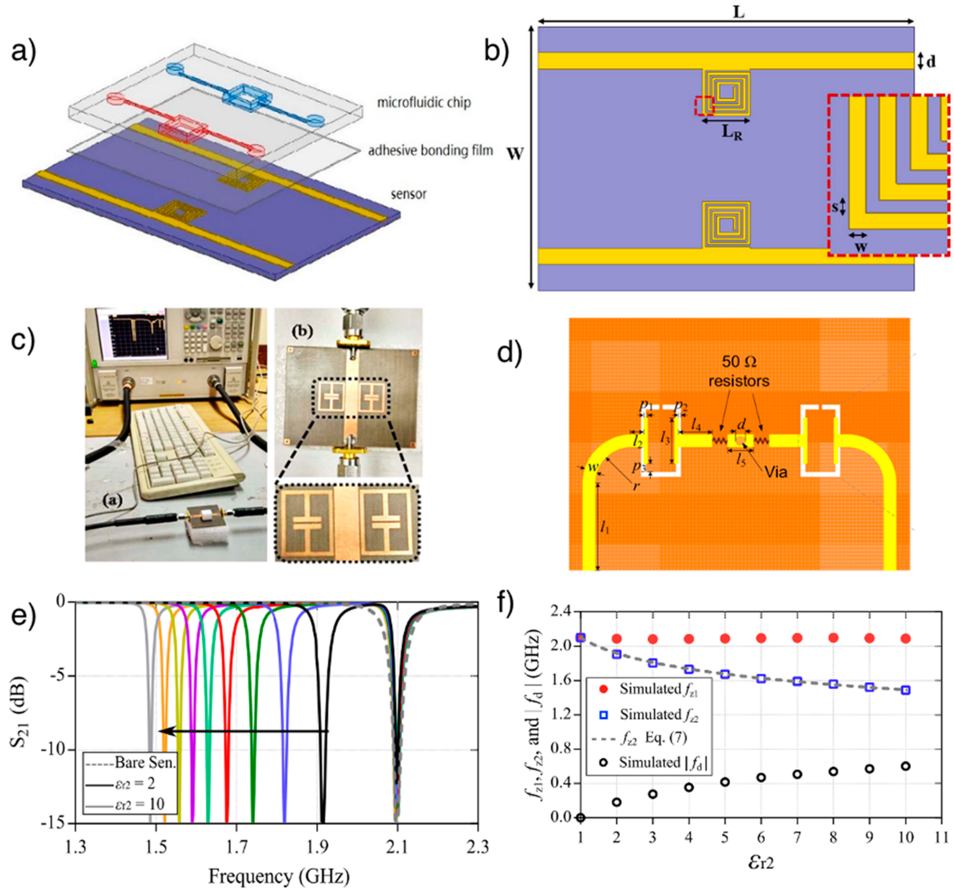

Figure 4. Examples of mitigating environmental noise for LC resonant sensors. (a) Diagram of spiral differential sensor with a microfluidic channel for liquid sample comparison measurements and (b) top view of differential spiral resonators (Reprinted with permission from ref 80. Copyright 2018 Springer Nature). (c) Electric LC resonant sensor run in differential format for subtracting environmental noise (Reprinted with permission from ref 83. Copyright 2021 IEEE). (d) Split ring resonator differential sensor (Reprinted with permission from ref 81. Copyright 2020 IEEE). (e) Bode plot of differential resonator output with two resonance dips and (f) frequency shift f unloaded resonator (red), loaded resonator (blue), and the difference between them (black) (Reprinted with permission from ref 79. Copyright 2018 IEEE).

sensors for wearable applications including low manufacturing costs and the capability to create a large sensor network.

Unlike off-body diagnostic sensors, wearable resonant sensors are subject to changing environmental conditions and positional changes to the reader which lead to increased noise. The magnitude of scattering parameters tends to be more sensitive to environmental noise than the resonant frequency and thus most wearable applications rely upon shifts in resonant frequency as the readout method. A few exceptions exist, such as a spiral resonant sensor attached to the wrist of an arm proxy that monitors pulsatile flow and hemodynamics.[16] Magnitude of signal change could be monitored for this resonator as the power source was wired directly to it, and it was an idealized static setup. Devices which rely upon inductive coupling of an external reader antenna cannot rely upon the magnitude of a scattering parameter as this is a function of the relative distance between the reader and antenna. Resonant frequency is solely monitored in these cases, e.g., for an embedded resonant bandage wound monitoring sensor[35] or tooth cavity sensor.[39]

CHALLENGES OF RESONANT BIOMEDICAL SENSORS

Several challenges inherent to resonators need to be addressed before seeing more widespread, practical use in biomedical applications. First, resonant sensors are extremely sensitive to environmental parameters, such as temperature and relative humidity which affect the dielectric properties of the materials of the sensor, obfuscating its resonant frequency response.[77] Sensitivity toward biological analytes tends to be small and leads to low signal-to-noise. Also, as resonant sensors are sensitive to bulk properties, rendering them specific or selective to analytes of interest are nontrivial tasks. Finally, contact-free resonant sensors inductively coupled with an external reader are sensitive to positional alignment between the reader and the sensor itself, which can also confound sensor response.[77] Each of these limitations needs to be addressed to ensure consistent sensor response. Efforts toward this are described next.

MITIGATE ENVIRONMENTAL EFFECTS USING DIFFERENTIAL SENSORS

Resonator frequency response can be confounded by changes in environmental parameters, e.g., temperature and relative humidity. This is because the relative permittivity of dielectric substrates, especially those with liquid dipoles such as biological samples, change with temperature which will shift the resonant frequency creating noise.[78] Environmental noise makes wearable sensor implementation especially difficult as the user will operate in diverse conditions versus on counter

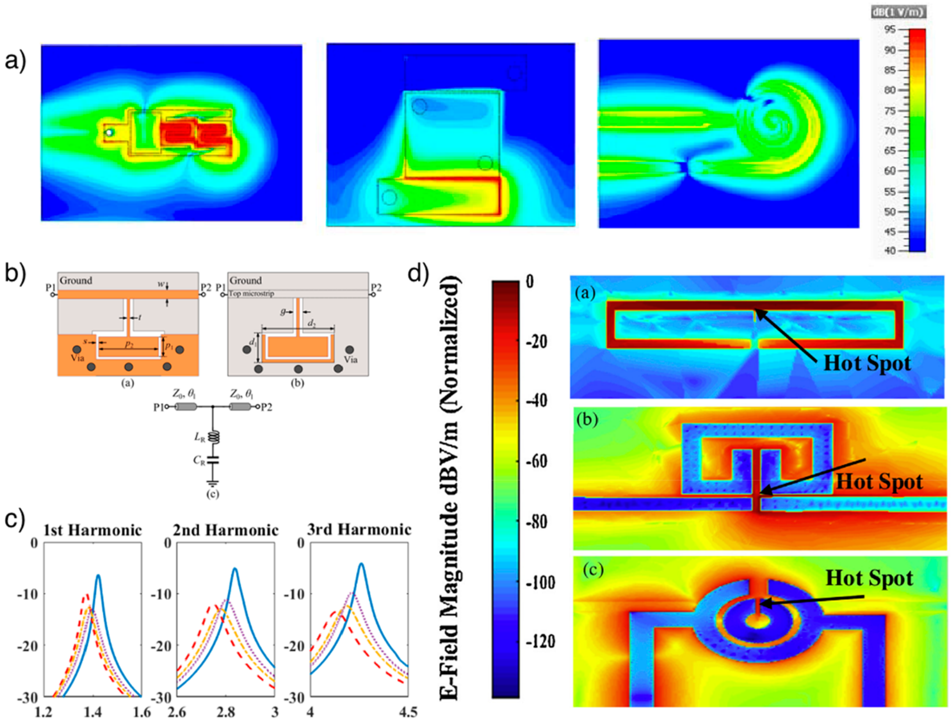

Figure 5. Examples of strategies to increase resonant sensor sensitivity. (a) Comparison of different sized resonators for sensitivity of electric field (V/m) from smallest (left) to largest (right) (Reprinted with permission from.86. Copyright 2018 IEEE). (b) LC resonator with increased sensitivity from designing it with a single sensitive capacitor for permittivity sensing (Reprinted with permission from ref 45. Copyright 2019 IEEE). (c) Demonstrated increased sensitivity of harmonic resonances with a mixture of different liquids (Reprinted with permission from ref 98. Copyright 2020 IEEE). (d) Sensitivity of electric field (V/m) of three different split ring resonator geometries (Reprinted with permission from ref 90. Copyright 2020 Elsevier).

diagnostics that can be better controlled. However, even laboratory-based tests can benefit from mitigation of environmental effects as small changes still occur.

The simplest method to separate environmental effects from resonator response is to use orthogonal sensors such as a temperature and humidity sensors. The effects of these environmental parameters on resonant frequency shift response are linear, and by the property of superposition, they can be subtracted from the response, isolating that change due to the parameter of interest. By calibrating the sensor response due to changes in environmental factors and using orthogonal sensors, the frequency response from the target analyte or physical change can be obtained. An obvious downside to this approach is the requirement for multiple sensors and data inputs for proper data analysis, which can make real time sensing challenging and increase cost.

A more economical solution to mitigate environmental noise is the use of a resonant sensor in a differential format. A differential resonator can detect the effects due cross-sensitivity by operating a pair of resonators with identical responses in tandem[79−81] (Figure 4). Differential resonators produce a single resonant frequency when the loads of the two resonators are equal to each other and have two resonant frequencies when the loads on the two resonators are different.[82] The two differential resonators can either be utilized to compare two separate samples, or to determine the environmental effects on the dielectric properties of the sensor materials (substrate, metal trace, etc.) and subtract out their collective effect on frequency shift.[83]

For differential resonant sensors it is imperative that the sensor architecture has a differential frequency response for accurate sensing. Both resonators in the sensor must be symmetrically loaded so that a single resonant notch in the frequency response of the sensor is found in an unloaded state.[84] That way, two notches in the frequency response will only appear when the symmetry between the two loads is broken by applying a sample or load to one resonator. For a wired resonant sensor this can be fabricated by inductively coupling a pair of resonant sensors to a single microstrip line.[79,80,83] However, for wireless resonant sensors there remains a challenge to ensure symmetry between two resonators as its positional alignment between the two resonators and a wireless reader will affect their resonant frequency and thus be difficult to obtain symmetry between them. Another design consideration for differential sensors is the proximity of the two resonators with respect to each other. It is optimal to have as little mutual coupling between the two resonators as possible to avoid inadvertently affecting the resonant frequency of one by adding a sample to the other. It is best to use a layout that provides enough physical space to prevent mutual coupling.[85]

■ INCREASE SENSITIVITY

Increasing sensitivity of resonant sensors is another important factor for biomedical applications. For resonators that monitor changes in capacitance this can be achieved by increasing the self-resonant frequency of the resonator.[86] As the self-resonant frequency increases, either the inductance or capacitance of the resonant sensor decreases. For distributed resonators that utilize a parasitic capacitance for resonance, this is usually accomplished by making a smaller inductor which decreases the metallic trace of the circuit and thus decreases the

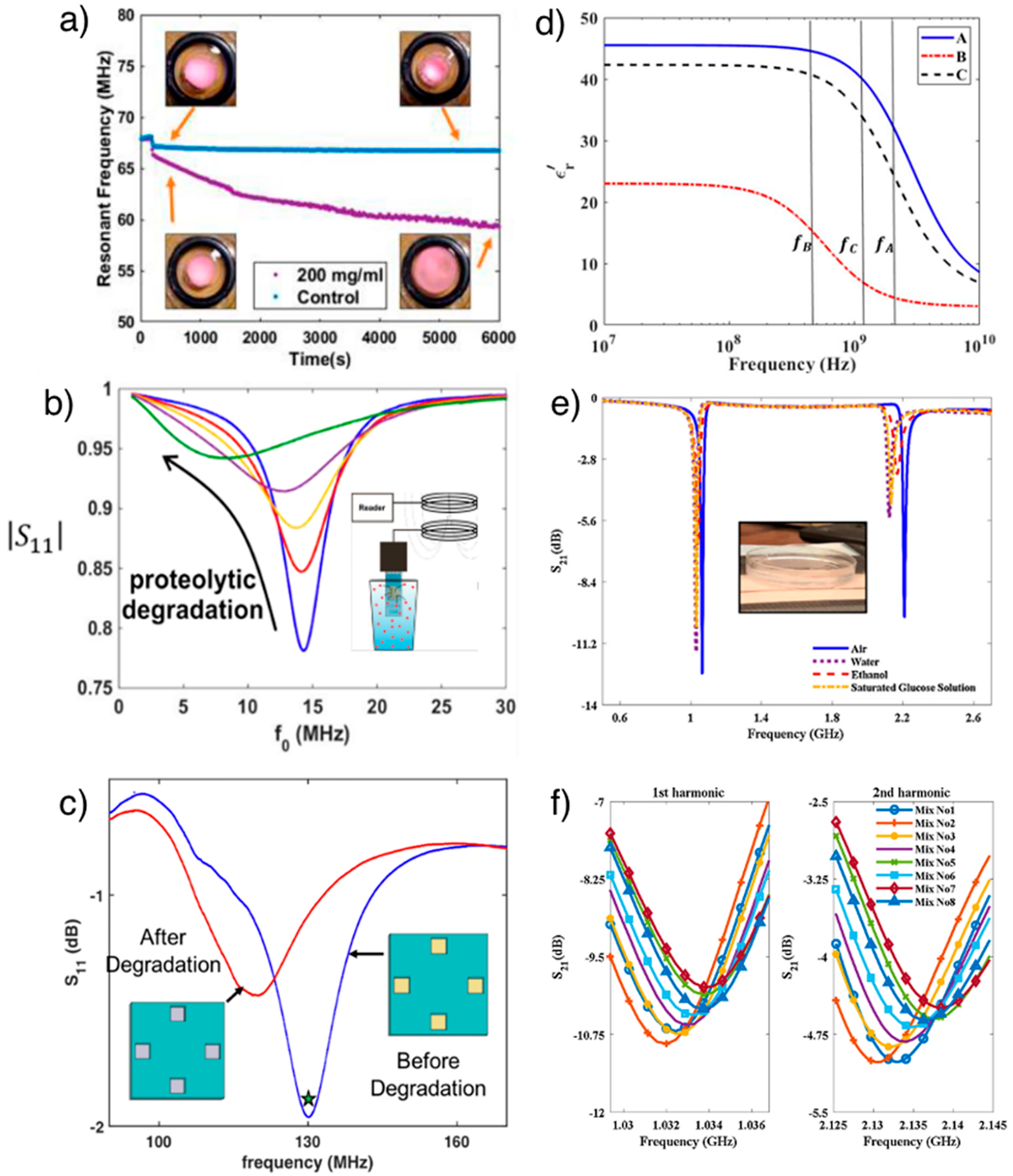

Figure 6. Examples of strategies to increase specificity of sensors: (a) Degradable hydrogel coating for detection of specific hydrolytic enzymes (Reprinted with permission from ref 100. Copyright 2018 American Chemical Society). (b) Degradable substrate for proteolytic specific activity (Reprinted with permission from ref 40. Copyright 2020 American Chemical Society). (c) Viral RNA detection via degradable substrate with gene circuit expressing reporter enzyme in vitro (Reprinted with permission from ref 42. Copyright 2022 American Chemical Society). Example to increase selectivity: (d) Different dispersions at various frequencies of materials for selective sensing (Reprinted with permission from ref 98. Copyright 2020 IEEE). (e) Pure species responses at two harmonic frequencies of different solutions and (f) the linearly additive responses of mixtures of those solutions (Reprinted with permission from ref 89. Copyright 2021 Elsevier).

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capacitive reactance.[87] This has been observed when comparing the sensitivity of three resonant glucose sensors where the smaller resonator with higher resonant frequency was demonstrated to be more sensitive toward changes in glucose concentration[86] (Figure 5a). If the resonant sensor has a discrete capacitance, then this can be directly minimized to increase sensitivity to capacitive changes[45] (Figure 5b). The downside to increased self-resonant frequency is the fact that conductivity and loss tangent increase with frequency.[10]

Another way to increase sensitivity is to utilize harmonic resonances. Harmonics for distributed resonant sensors arise because integer multiples of the self-resonant frequency also resonate like octaves on a string instrument. Another interesting characteristic of harmonics is that the relative frequency shift also increases in integer multiples of the fundamental frequency shift[88] (Figure 5c). Thus, a low-frequency resonator, less susceptible to loss, can be deployed and its harmonic resonances analyzed with a higher sensitivity.[89] This has been used for monitoring hemodynamics with a wearable resonant sensor device that doubled the sensitivity of the sensor by monitoring its first harmonic.[16] In practice, however, care must be taken when analyzing harmonics as, depending on the loss tangent of the substrate and the frequency range of a reader, it can be difficult to identify and analyze harmonics.

Besides increasing self-resonant frequency or analyzing harmonics of a resonant sensor, one of the most effective ways to increase sensitivity is to increase the electric field around the resonator. As mentioned previously, environmental factors, especially loss tangent, in biomedical applications greatly affect the sensitivity of resonant sensors. Increasing the electric field around the resonator can increase the sensors' abilities to polarize molecules in the material under test and thus increase sensitivity.[90] It also increases the quality factor of the resonant sensor, making it more sensitive in lossy environments. An increase in sensitivity via increasing electric field around the resonator has been demonstrated for both passive resonant sensors[80,86,90] and active resonant sensors[91−94] (Figure 5d).

Up to this point only resonant sensor design and/or analysis have been considered to increase sensitivity for biomedical applications. However, the conversation around resonant sensor sensitivity would be incomplete without a discussion of the dielectric properties of the sensing sample. Since the resonant frequency is inversely proportional to the square root of the relative permittivity of the material under test, the incremental shift in frequency will decrease as the relative permittivity increases.[90] Since biomedical applications often monitor samples with a high water content, the baseline relative permittivity is fairly high from values greater than 50 for most human tissues[95] all the way to 80 for aqueous samples such as blood. If there is a large change in relative permittivity, e.g., tumorous versus normal breast tissue,[96] then a significant resonant frequency shift can be expected. However, if there are minor changes in relative permittivity, such as blood glucose levels,[97] then the signal-to-noise ratio relative to the frequency shift needs to be optimized to develop a sensitive sensor. In several cases, however, it is not currently feasible for certain biomedical applications to implement resonant sensors due to many environmental sources of noise which can obscure readings with relatively small frequency shifts.

INCREASE SPECIFICITY AND SELECTIVITY

Resonators utilize radio and microwave frequencies which generate long wavelengths in the electromagnetic spectrum (Figure 1), which translates to larger electric fields and measurement of bulk properties of a sample. This is ideal for measuring widespread properties such as tissue dielectric,[34] intracranial pressure,[99] and temperature.[53] However, because their sensing region can be up to a few centimeters, it is difficult to render resonant sensors specific to a single analyte. Rendering a sensor specific to a smaller target, e.g., a dissolved molecule in a mixture of chemical species, requires adding a transduction element that will amplify any chemical or biochemical signal. This has been demonstrated using degradable coatings for the detection of hydrolytic enzymes[40,100] (Figure 6a,b). In another study the target analyte was viral RNA which was a detected biochemical using a riboregulator called a toehold switch which expressed a protease in the presence of target RNA[42] (Figure 6c). Subsequently the resonator transduced the presence of the target RNA via degradation of a gelatin hydrogel coating. For resonant sensors to become more specific, similar approaches using a secondary transduction mechanism to amplify chemical/biochemical interactions will need to be included in the sensor design.

Beyond specificity, there is also a need to address resonant sensor selectivity, that is the identification of multiple species, especially in a complex mixture. Some work has been done to use arrays of resonant sensors to transduce mixtures of chemical species in solution by using resonant sensors with different operating frequencies[89] (Figure 6d−f).This was able to discriminate relative proportions in a mixture of chemical species. The working principle is that chemical species will have different polarization relaxation dispersions at different frequencies. By analyzing at different frequencies, a fingerprint of the mixture can be taken which is a function of the relative proportions of species in solution. This work could lead to potential to create biomedical sensors that can fingerprint complex biological samples for diagnostic purposes.

MITIGATE POSITIONAL ALIGNMENT SENSITIVITY

A major challenge in the implementation of resonant sensors for wearable applications is the sensitivity of resonant frequency to the positional alignment between the reader coil and sensor. Unlike RFID tags which utilize inductive coupling for wireless power transfer to power a chip, resonant sensors use inductive coupling for both wireless power transfer and sensor transduction. The relative strength of induction between the two coils is calculated using the coupling coefficient, k, which is defined as the ratio of the mutual inductance divided by the square root of the product of the self-inductances of the coils, where $k = 1$ means perfect coupling. Since mutual inductance is a function of the proximity and orientations of the magnetic field of the first coil, the actual mutual inductance will be a function of how close the two coils are plus the relative orientation of the field.[74]

A recent study demonstrated that the size of the resonant could be exploited to mitigate the positional sensitivity in a wearable application.[86] It was concluded that to overcome measurement noise from positional sensitivity, a smaller resonator architecture should be used. As the sensor increases in size, so do its magnetic fields which become more prone to

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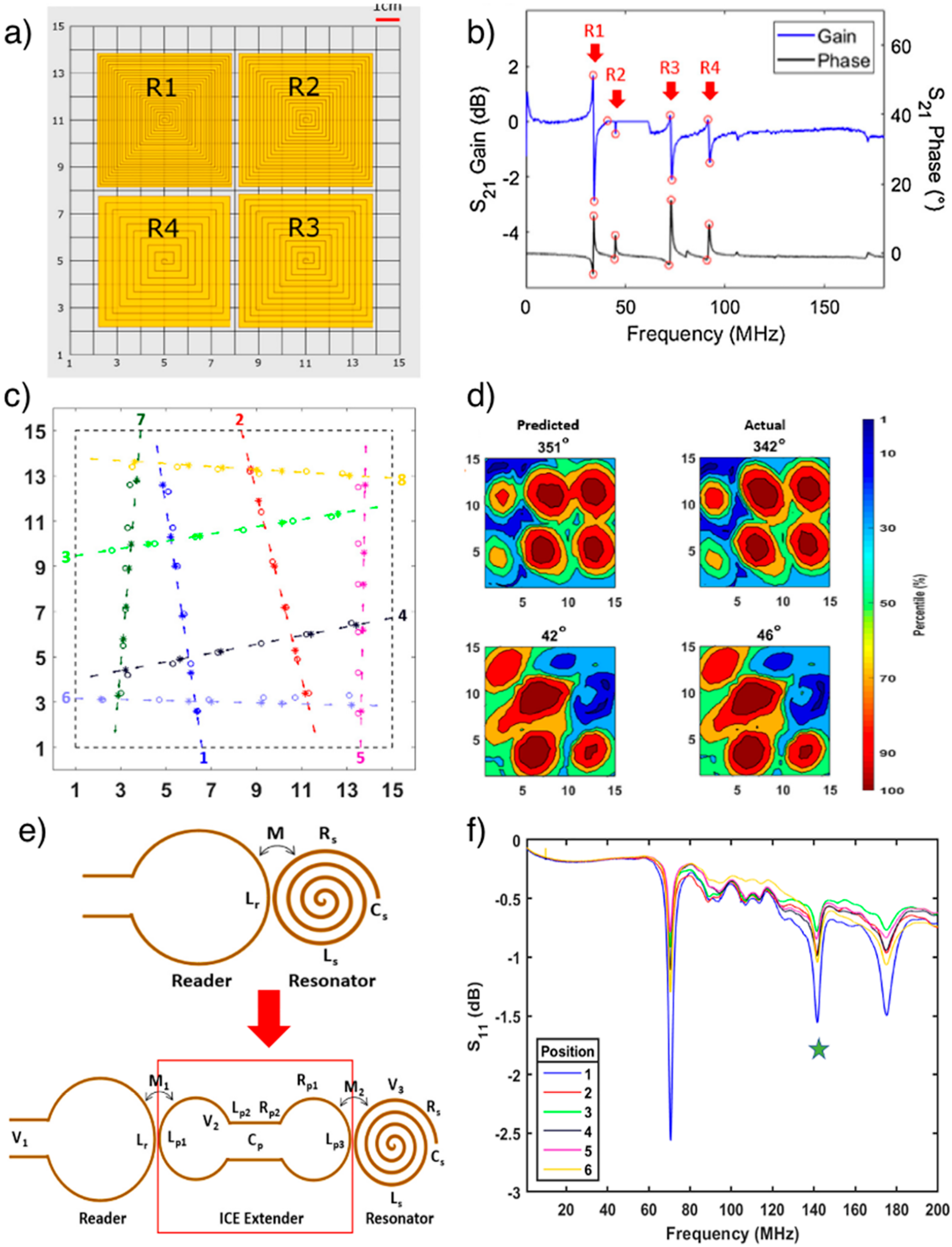

Figure 7. Strategies to mitigate positional sensitivity of wireless inductively coupled LC resonant sensors. (a) Resonator array for positional tracking of reader antenna and (b) Bode plot with resonant frequencies of array depicted. (c) Trajectories of reader across resonator array and (d) predicted heat maps of reader antenna position (Reprinted with permission from ref 101. Copyright 2020 Elsevier). (e) Regular LC and ICE-LC with reader antenna schematics and (f) Bode plot depicting stable resonant frequency at different positions between reader antenna and ICE-LC sensor (Reprinted with permission from ref 102. Copyright 2021 Elsevier).

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incomplete inductive coupling compared to a smaller resonator. However, the trade-off for using a smaller resonant sensor is that it generally comes with a higher resonant frequency, which makes it more susceptible to loss (Figure 1) which can make it impractical for use with biological samples.

Some recent studies have attempted to engineer the architecture of the resonant sensor system to overcome positional sensitivity. In one study, an array of resonant sensors was used to locate the relative position of the reader and resonator array (Figure 7a,b). The array consisted of one sensing element and four positional detection elements. The reader was scanned at different positions above the array of positional detection elements and further refined using interpolation between positions to create a map of the array response as a function of reader position (Figure 7c,d). In this way the position of the reader and positional array could be calculated which could then be used to calibrate the positional sensitivity of the reader and sensing element and subtract the positional effect on the resonant frequency.[101] Although a prototype of using such a resonator array was demonstrated, the process of generating an initial data set for the positional elements and the reader is tedious and the algorithm implemented to track the relative alignment between the two is computationally laborious. A more elegant approach was taken by decoupling the inductive coupling and parasitic capacitance between the reader and resonant sensing element altogether. Instead, an intermediate element was used to couple with the reader on one end and with the sensor on the other end. The intermediate element and the resonant sensor were fixed together, which meant that the coupling coefficient between the two were kept constant. This intermediate element, called an inductively coupled extender (ICE), was able to create a wireless resonant sensor that was insensitive to positional alignment between the reader and sensor[102] (Figure 7e,f). Further work needs to be done to implement the aforementioned studies into wearable devices to determine their practicality in biomedical applications.

■ OUTLOOK FOR RESONANT SENSORS IN BIOMEDICAL APPLICATIONS

LC resonators have the potential to make significant impact in the growing trends of telehealth, including diagnostics and wearable health monitors with development of low-cost sensors that can be additively manufactured on top of existing devices and infrastructure.[28] Resonators have been demonstrated for a number of biomedical applications in the literature and could replace many of the existing sensors including three-electrode systems and bioimpedance spectroscopy. One example would be replacing the use of broadband or wideband microwave sensors which require expensive analyzers to perform large frequency sweeps to measure dielectric properties of a sample, which is currently applied to detection of malignant tumors.[103−105] Instead, LC resonators, with their narrowband resonance, focus on a smaller range of frequencies allowing for lower cost VNAs and custom readers.[30] However, sensitivity toward the analyte and selectivity would need to be optimized before resonators can be used in clinical practice.

Wearable resonant sensors have distinct advantages over current sensor offerings that make them a compelling area of continued research and development. These include the ability to be wirelessly interrogated through opaque nonmetallic materials[29] as well as no need for an onboard power supply. This allows them to be designed as flexible devices that can be adhered conformally to the skin and be monitored through clothes or even implanted inside tissues. Additionally, their facile fabrication (allowing for roll-to-roll fabrication) gives them a cost-competitive advantage to other sensors that require traditional integrated circuits. This would allow for more widespread application of sensors, such as multisite temperature monitoring under bulky personal protective equipment to build a better model of heat stress. As outlined in this perspective, for resonators to gain more widespread adoption in wearable applications, robust responses need to be achieved in varying environmental conditions plus the positional alignment sensitivity of the external reader to sensor needs to be mitigated. Other factors that were not explicitly covered in this perspective, but should also be addressed, include the effect of flexiblility of conformal sensors on their operation as well as methods to improve the detection limit and linear response range for robust operation. When a transducing element that changes the permittivity in response to target is incorporated, the inherent limitation of the transducing element should also be accounted.

■ CONCLUSION

Resonant sensors have advantages over other sensing modalities, especially wired or traditional optical techniques, for biomedical applications that are on-body and enclosed; they also find utility in off-body diagnostic assays. They operate in a tissue transparent radio frequency range, are low cost to fabricate, have a fast response time, can be read contact free, and can be rendered sensitive to specific analytes. However, some design considerations and challenges of these sensors are mitigation of environmental noise, increasing sensitivity of a biological sample with high conductivity, rendering the resonance response specific and/or selective to the analyte of interest, and decreasing the positional sensitivity between reader and sensor for wearable applications where the reader is removed and repositioned throughout the course of study.

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Notes

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