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Original Article

Single-Ended and Differentially Operated Microwave Microfluidic Sensors for Biomedical Applications

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Abstract

Background: This research is focused on the design of highly sensitive microfluidic sensors for the applications in liquid dielectric characterizations including biomedical samples. **Methods:** Considering the narrow-band operation of microfluidic sensors based on microwave resonators, in this study, microfluidic sensors based on the variation of transmission phase in microwave transmission lines (TLs) are proposed. It is shown that among different microwave TLs, slot-lines are an appropriate type of TL for sensing applications because a major portion of the electromagnetic (EM) field passes above the line, where a microfluidic channel can be easily devised. **Results:** The proposed concept is presented and the functionality of the proposed sensor is validated through full-wave EM simulations. Moreover, the effects of the dimensions of the microfluidic channel and the thickness of the substrate on the sensitivity of the sensor are studied. Furthermore, taking the advantages of differential circuits and systems into account, a differential version of the microfluidic sensor is also presented. It is shown that the sensitivity of the sensor can be adjusted according to the application. Specifically speaking, the sensitivity of the proposed microfluidic sensor is almost linearly proportional to the length of the channel, i.e., the sensitivity can be doubled by doubling the channel length. **Conclusions:** In this research, it is shown that using slot-line TLs highly sensitive microfluidic sensors can be designed for the applications in liquid dielectric characterizations, especially for biomedical samples where small variations of permittivity have to be detected.

Keywords: *Differential sensor, microfluidic sensor, slot-line*

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Introduction

Microwave sensors have a significant role in electronic automation, biomedical, and industrial applications.[1,2] Microwave sensors have many advantages compared to optical/photonic sensors such as low fabrication and measurement costs, wireless connectivity, compatibility with planar technologies, high sensitivity, and robustness.[3] Among different microwave sensors, planar sensors have been used in many applications such as displacement and rotation sensors[4-10] conformal[11] and wearable sensors,[12] integrated sensors,[13] lab-on-a-chip sensors,[14] microfluidic sensors[15-21] etc. The versatility of these sensors is also due to their small size. Moreover, microwave resonator sensors are very sensitive to the properties of their surrounding medium due to their high Q-factor resonance. The high sensitivity of planar microwave resonators is very promising for the application in material sensing including microfluidic and biosensing applications[22,23] and accurate identification of chemical and biological solid and liquid samples.[23-27] To this end, by introducing a chemical or biological material under test (MUT) in the surrounding area of a microwave resonator, the frequency response (usually the frequency or the amplitude) of the resonator is altered.[1] Therefore, unknown chemical or biomedical materials can be identified.

In many applications, especially biomedical identifications, conducting a diagnostic laboratory test using a very small sample of the MUT (such as blood) is crucial.[28] To satisfy this requirement, microfluidic sensing has attracted significant attention. For instance, in[29] and[30] microfluidic channels were designed to deliver fluid

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samples to an array of resonators, which results in a significant change in the resonance frequency of the resonators. Despite its high sensitivity, due to array configuration, this method requires a relatively large amount of liquid sample. To reduce the required fluid sample, in[31] a microfluidic channel mounted on a spiral resonator coupled to a microstrip line was used for liquid sensing. This device presented a bandpass behavior with limited accuracy for dielectric characterization.

To address this issue different variations of microfluidic sensors, especially based on metamaterial resonators have been proposed for instance in.[15,20] However, despite their compactness, the proposed sensors suffer from limited sensitivity. A short literature review on this concept will be presented in the following section. Novel microfluidic sensor based on slot-lines is then presented in the Methods Section. Results Section provides electromagnetic (EM) simulated behavior of the proposed sensor. The section also suggests various methods to increase the sensitivity of the sensor, which are supported by full-wave EM simulation results. Moreover, the application of the proposed sensors in differential form is presented in results section. Finally, comparison to the state-of-the-art microwave microfluidic sensors and a summary of the study is presented in the last section.

Literature review

Among different types of microwave resonators, metamaterial-inspired resonators benefit from very small size and high-Q resonance. To benefit from the unique features of metamaterial resonators, a microfluidic sensor based on a single split-ring resonator (SRR) coupled to a microstrip line has been proposed in.[15] An illustration of the sensor is shown in Figure 1a, where microstrip line and the loading SRR are both implemented on the top metal layer (shown in yellow color), while the ground plane (in orange color) is on the back side of the substrate. In the presented sensor, a microfluidic channel was devised in the capacitive gap of the SRR, where a very strong and localized electric field exists. As a result, applying a liquid sample to this capacitive gap modifies the resonance frequency and quality factor of the resonator, from which the complex permittivity of mixtures can be determined. However, since the length of the capacitive gap and as a result, the length of the microfluidic channel affecting the SRR was limited, the sensitivity of the device was not enough to discriminate small changes in the permittivity of a sample under test. To address this issue, a microfluidic sensor based on a microstrip line loaded with a complementary SRR (CSRR) was presented in.[20] As shown in Figure 1b, again the microstrip line is implemented using the top copper layer (in yellow), while the CSRR (in white) is etched in the ground plane (in orange) on the back side of the substrate. It is clear that the capacitive gap of a CSRR is much longer than the capacitive gap of an SRR resonating

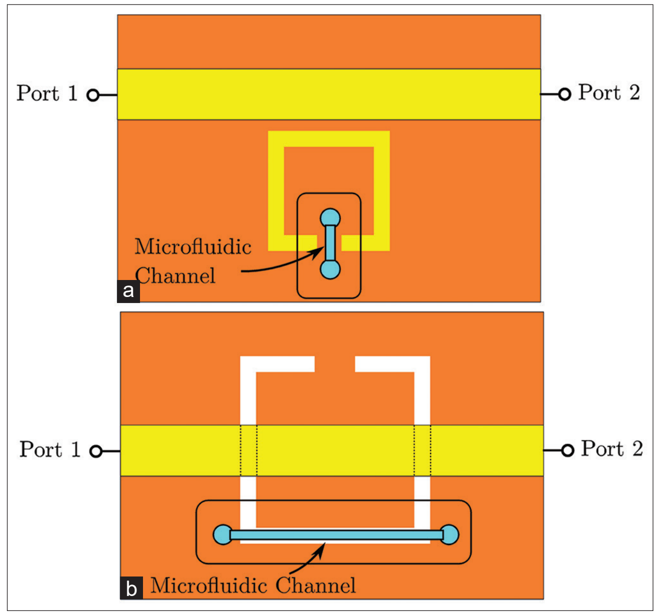

Figure 1: An illustration of the microfluidic sensors based on (a) an split-ring resonator-loaded microstrip line and (b) a complementary split-ring resonator-loaded microstrip line

at the same frequency. As a result, a longer microfluidic channel is devised and eventually the presented sensor benefits from higher sensitivity to the permittivity of the MUT. However, the length of the microfluidic channel cannot be arbitrarily selected since it is still limited to the capacitive area of the CSRR. It is clear that enlarging the dimensions of the CSRR may not be possible in some applications, especially when permittivity characterization at higher frequencies is desirable.

To address this limitation, this article presents a microfluidic sensor based on a slot-line loaded with a microfluidic channel. The advantage of the proposed sensor is twofold: (1) Depending on the required sensitivity in each application, the length of the microfluidic channel can be arbitrarily chosen. (2) While sensors based on resonators generally benefit from higher sensitivity, the permittivity of the sample under test can be characterized in a single frequency. In contrast, for wideband dielectric characterization of biomedical fluid samples, the presented sensor in this study can be excited over a wide frequency band.

Designing a differential version of the proposed microfluidic sensor is another contribution of this research. Introduced error due to EM interference and environmental factors such as temperature and humidity is one of the major issues in almost all sensing and measurement systems. An efficient method to avoid such sensing and measurement errors, which in most cases have a common-mode nature, is to use differential sensing and measurement systems.[32-38] Moreover, differential sensors can be used to accurately compare a MUT with a reference material. It is demonstrated in this article that the proposed slot-line

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microfluidic sensor can be easily used in a differential form, not only to avoid environmental noise and adverse effects of ambient conditions but also to facilitate the relative measurement of the dielectric constant of two samples, for instance, to differentiate between the blood sample of a healthy person and that of a diabetic patient.

Methods

Dominant methods in microwave dielectric characterization of solids and fluids are based on the variation of frequency or amplitude of a signal passing through a resonator-loaded transmission line (TL).[36] To address the limitations of such dielectric characterization methods, recently, a novel sensor based on meandered microstrip lines has been proposed in.[39] One of the main advantages of the presented sensor in[39] is that a high (adjustable) sensitivity to small changes in the permittivity of the MUT is achieved. However, the high sensitivity is obtained at the cost of loading the microstrip line with relatively large samples of MUT. The reason behind this limitation will become clear by exploring the EM field of the utilized microstrip line. Microstrip lines are one of the most popular types of planar TLs since they benefit from a very low-cost fabrication and easy integration with passive and active microwave devices. An illustration of the cross-section of a microstrip and the loading MUT is shown in Figure 2a. As shown in figure, the microstrip line consists of a conductor strip, which is printed on the top side of a dielectric substrate with a relative permittivity ϵ_r, and a metallic ground plane on the opposite side of the substrate. In this configuration, the effective permittivity of the microstrip line is determined by the substrate as well as the MUT on top of the microstrip line.

As a result, variation of the permittivity of the MUT leads to changes in the effective permittivity of the TL, and eventually changes the phase of the transmission coefficient. Thus, the MUT can be characterized by measuring the transmission phase of the structure.[39]

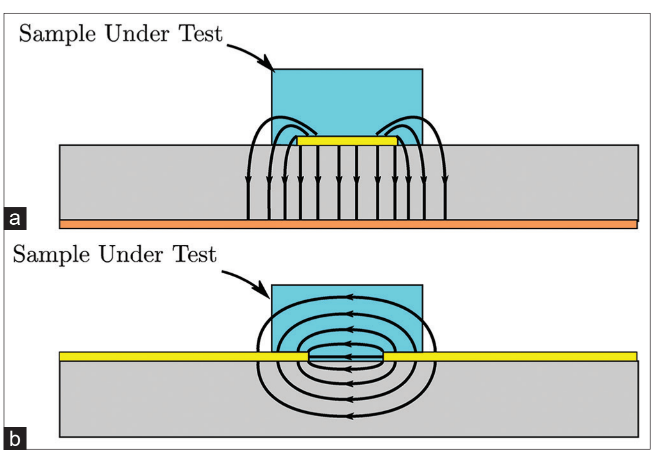

Figure 2: An illustration of the cross-section of (a) a microstrip line and (b) a slot-line, both loaded with the material under test. The figure also shows the electric field lines in both cases

However, as shown in the figure, a major part of the electric field in the microstrip line is contained within the substrate region. This is true even when the permittivity of the MUT is higher than the permittivity of the substrate because the excitation voltage is applied between the microstrip line and its ground plane. Therefore, the variation of the propagation phase due to the changes in the permittivity of the MUT is not significant.

To address this issue, i.e., to increase the sensitivity of the sensor to the permittivity of the MUT, slot-lines are used in this work. An illustration of the cross-section of a slot-line and the loading MUT is shown in Figure 2b. Again, the working principle of the proposed sensor is based on the phase variation in transmission coefficient caused by a change in the permittivity of the MUT. However, in this case, as shown in the figure, the slot-line consists of a pair of conductor planes that are both printed on the top side of a dielectric substrate, while no metallic ground plane on the opposite side of the substrate exists. Comparing the electric field lines for the slot-line and the microstrip line reveals that the electric field on top of the slot-line is stronger and more electric field lines (compared to the microstrip line sensor) pass the MUT. Thus, the variation of the propagation phase due to changes in the permittivity of the MUT is more significant in the slot-line sensor. This in turn means that smaller samples of MUT are required for permittivity determination.

An illustration of the proposed slot-line sensor for microfluidic sensing is shown in Figure 3. In this structure, the slot-line is partially covered by the liquid under test which is flowing in a microfluidic channel, which is devised by polymethyl siloxane (PDMS) material. Therefore, the phase constant of the line is a function of the permittivity of the fluid under test. It is important to note that unlike in the case of microfluidic sensors based on CSRR resonators, the length of the microfluidic channel

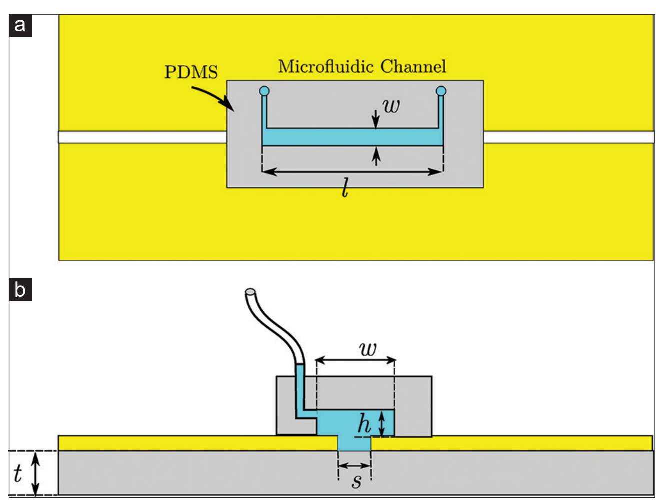

Figure 3: (a) Top view and (b) cross-section of the proposed slot-line sensor for microfluidic sensing based on a slot-line loaded with a microfluidic channel

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is not limited by the size of the resonator, but the length of the channel can be arbitrarily selected. This is an important feature because depending on the application and the required sensitivity, one can choose an appropriate channel length. In short, a longer microfluidic channel will result in a higher sensitivity, which is appropriate for sensing small changes in permittivity. Such a high sensitivity sensor can be used in applications such as sensing glucose in blood samples in which the variation in the permittivity is limited to a couple of percents. On the other hand, to avoid saturation of the sensor in applications such as determining isopropanol concentration in water, where high variations in the permittivity of the fluid under test are expected, a short microfluidic channel must be used. Note that when utilizing the sensor an ambiguity may arise if the phase variation goes beyond 360° or 2 π radian. Although, methods such as time delay measurement can be used to avoid the ambiguity between an angle φ and $2k\pi + \varphi$, it is more convenient to constrain the variation of phase between 0 and 2 π.

Results

Validation of the proposed sensor

To validate the proposed microfluidic sensor, the phase response of the sensor for different values of the permittivity of the fluid under test is simulated using the Ansys HFSS full-wave simulation software package. A 1 mm thick Rogers RO5880 substrate with a relative permittivity of 2.2 is used as the substrate. The slot with s = 0.1 mm is chosen, while a 4 mm by 4 mm microfluidic channel is formed by PDMS material. It is important to note that the material used for forming the microfluidic channel has to be biocompatible. To this end, a variety of materials such as silicon, glass, and PDMS can be used. Among these materials, PDMS is vastly used for the fabrication of microfluidic channels because, in addition to being biocompatible, it has good mechanical strength. Moreover, its soft form can be used along with mold tools for mass production of microfluidic channels with good repeatability.

Figure 4 shows the simulated transmission phase $\angle S_{21}$ versus the operating frequency (from 5 to 7 GHz) of the slot-line for different values of fluid relative permittivity in a wide range from 1 to 40. The simulation results clearly show that the transmission phase is a function of the permittivity of the fluid under test. Therefore, in short, the measured transmission phase of the structure can be used for determining the permittivity of the fluid under test.

Adjusting the sensitivity of the proposed sensor

To appreciate the sensitivity of the proposed sensor, the transmission phase of the sensor versus the operating frequency for fluid sample with a permittivity of $\epsilon_r = 2$, compared to an empty channel (permittivity of $\epsilon_r = 1$) for a microfluidic channel length of l = 5 mm is simulated and

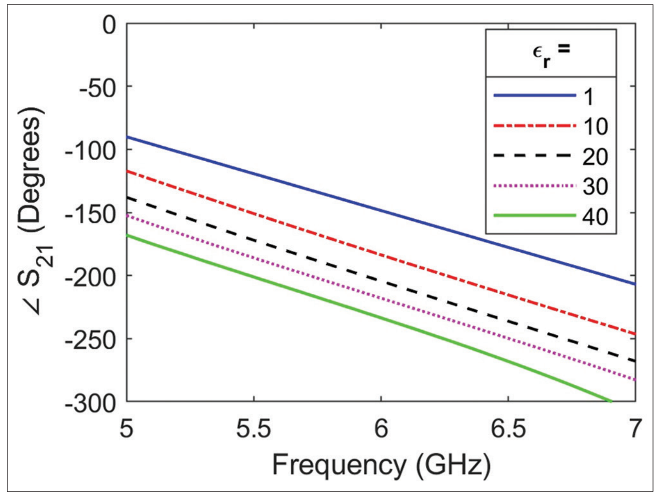

Figure 4: The simulated transmission phase ∠S21 versus frequency for different values of fluid relative permittivity

plotted in Figure 5a. The results show that the transmission phase of the sensor changes by approximately 5° when the channel is filled with the fluid under test, which is enough sensitivity for many applications.

However, as mentioned earlier, for the applications that the relative permittivity of fluid under test is relatively low or very high sensitivity is required a longer microfluidic channel can be used. For demonstration, the transmission phase of the sensor versus the operating frequency for a fluid sample under test with a permittivity of $\epsilon_r = 2$ for different lengths of the microfluidic channel is shown in Figure 5b. The phase response of the sensor for an empty channel (i.e., $\epsilon_r = 1$) is also plotted as a reference. The figure clearly shows that the sensors with longer channel length present higher sensitivity (greater phase difference with respect to the reference sample). For instance, the microfluidic sensor with a channel length of l = 25 mm shows a 25 degree phase shift for one unit change in the permittivity of the fluid under test. In short, the results show that the sensitivity of the sensor can be adjusted according to the application. Specifically speaking the sensitivity of the proposed microfluidic sensor is almost linearly proportional to the length of the channel, i.e., the sensitivity can be doubled by doubling the channel length. This is an advantage of the proposed sensor compared to the sensors based on CSRR where usually the length of the channel is limited to the size of the CSRR. Moreover, since the sensor is not resonance-based it can be operated over a wide frequency band. Therefore, characterization of the fluid under test can be performed at multiple frequencies or a wide frequency band.

Another efficient method to increase the sensitivity of the sensor is to use a thin and/or low permittivity substrate for the slot-line. Using a thin or low-permittivity substrate results in a higher number of electric field lines above the substrate where the microfluidic channel is devised. Thus, a sensor with higher sensitivity is achieved. This is

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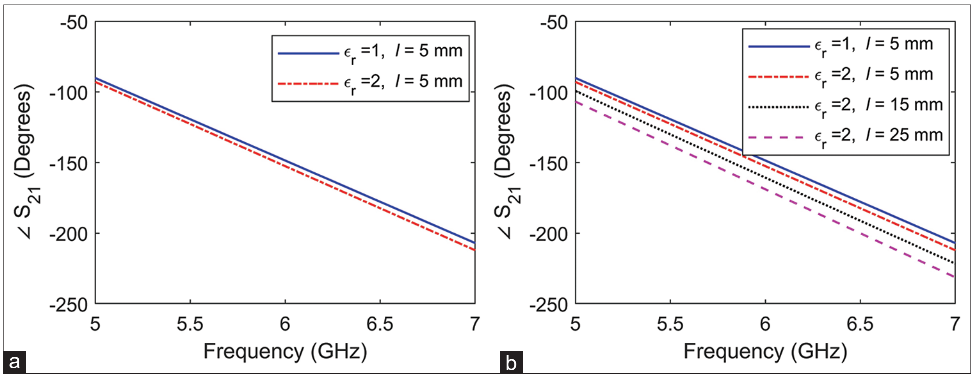

Figure 5: The transmission phase of the sensor versus the operating frequency (a) for a fluid sample with $\epsilon_r = 2$ compared to an empty channel (permittivity of $\epsilon_r = 1$) for the microfluidic channel with the length of l = 5 mm, and (b) for the same fluid under test (with a permittivity of $\epsilon_r = 2$) for different lengths of the microfluidic channel from 5 mm to 25 mm

demonstrated in Figure 6 by simulating the transmission phase difference (with respect to the empty microfluidic channel) versus the substrate thickness at three different frequencies. As shown in the figure, the sensitivity of the sensor (Δϕ) decreases as the thickness of the substrate is increased.

Note that as presented in the introduction, many microfluidic sensors based on a shift in the resonance frequency have been already presented by other research groups. One of the drawbacks of such sensors is that the sensor has to be operated over a band of frequency. Therefore, a relatively elaborate frequency sweeping readout circuit is required. In contrast, the sensor proposed in this study works based on the variations of phase, thus, is operated at a single frequency. This feature significantly simplifies the readout circuit. Moreover, as it is clear from the results presented in Figure 6, depending on the application the operating frequency can be changed to adjust the sensitivity.

Also note that the presented sensor is a two-port network that operates based on the variation of the phase of S_{21}. However, if the slot-line is short circuited from one end, a one port network is achieved that resonates at the frequency at which the length of the TL is a quarter wavelength. In this configuration, when the permittivity of the fluid under test is changed, the effective permittivity of the TL, and as a result, the resonance frequency is changed. Therefore, the structure can be used as a resonator-type microfluidic sensor, in which variations in the permittivity of the fluid under test can be detected by monitoring the resonance frequency of the structure.

Differential microfluidic sensor based on slot-lines

Differential sensors benefit from more accurate results compared to single-ended structures. They usually use two independent sensing elements: One for the reference sample and the other one for the sample under test. The typical output variable in differential sensors is one or more properties of the differential transmission coefficient, i.e., the sensing can be based on changes in the frequency, phase, or amplitude of the transmitted or reflected signals, and the input variable of the sensor is the difference between the permittivity of a reference sample (rather than empty channel) and a sample under test.

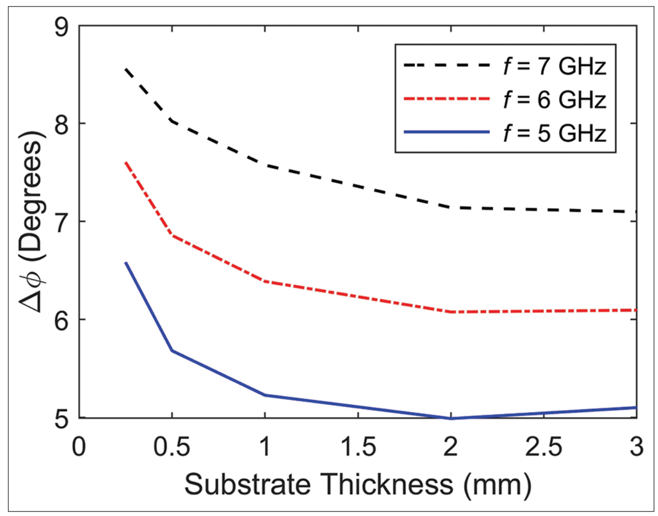

Figure 6: The simulated transmission phase difference Δϕ (with respect to the empty microfluidic channel) versus the substrate thickness at three different frequencies *f* = 5, 6, and 7 GHz

Considering the advantages of differential sensors, this section is devoted to the development of a differential microfluidic sensor based on the slot-line sensor of the previous section. An illustration of the proposed differential sensor is depicted in Figure 7. The structure consists of two separate slot-lines: One for the reference microfluidic channel and the other one for the fluid under test. In this structure, the reference sample and the sample under test are located in two channels in two separate slot-lines, therefore, when the permittivities of the reference sample and the fluid under test are identical, the phases of the two transmitted signals are equal. However, when a difference between the permittivities of the reference sample and the fluid under test exists, a phase difference between the two transmitted signals is observed. Thus, in short, the permittivity of the fluid under test with respect to the

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reference sample can be determined by measuring the phase difference between the two signals. Such differential sensors can be very handy in biomedical applications, especially to differentiate fluid samples such as blood from a patient with those of a healthy person.

To validate the concept, simulated phase difference $\Delta\phi$ between the transmission coefficients of the two differential lines versus the permittivity of the fluid under test is shown in Figure 8. Note that the sensitivity analysis performed in the previous section is also valid for the differential sensor presented in this section. That means, the sensitivity of the differential sensor can be adjusted by choosing an appropriate channel length.

A comparison with the state-of-the-art microwave microfluidic sensors may highlight the advantages of the proposed sensor. However, such comparison is not straightforward because except in the case of the sensor presented in,[39] the principle of operation of other permittivity characterization sensors found in the literature is based on a variation in the resonance frequency or amplitude of a resonance. Also, as mentioned in,[39] comparing the sensor presented in[39] with other sensors is not concluding, since the sensitivity of the proposed sensor can be made as high as required by simply increasing the length of the meander lines. In a similar manner it can be argued that comparing the sensor presented in this work with those based on a shift in the frequency or amplitude of resonance is not concluding because the sensitivity of the sensor can be increased as high as desired simply by increasing the length of the slot-line and the corresponding microfluidic channel. Therefore, the proposed sensor in this work is solely compared with the one in.[39] It is worth noting that a comprehensive (but nonconcluding) comparison between the sensor in[39] and other microwave microfluidic sensors can be found in.[39]

Note that in order to have a fair comparison, both sensitivities should be normalized to the length of the channel. In the case of the sensor presented in,[39] the phase shift $\Delta\varphi$ = 415.6 degrees is achieved by a meandered TL of length l = 778.75 mm. Therefore, the normalized sensitivity is S = 415.6/778.75 = 0.534. In contrast, the normalized sensitivity of the proposed sensor in this paper in its worst case (i.e., at f = 5 GHz) is S = 5°/5 mm = 1, which is almost double that of the sensor in.[39] Moreover, it is clear from Figure 6 that the sensitivity of the proposed slot-line sensor can be increased to S = 8°/5 mm = 1.6 (almost three times that of[39]) just by increasing the operating frequency to f = 7 GHz.

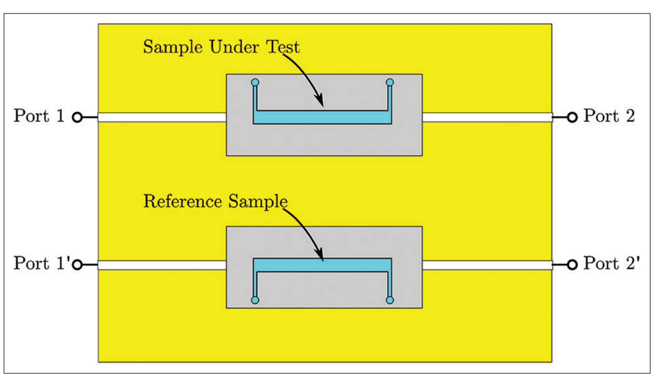

Figure 7: An illustration of the proposed differential microfluidic sensor

Conclusions

In summary, it has been shown that in contrast to a microstrip line for which most of the EM field is confined in the substrate area, a major part of EM field lines of a slot-line is located above the TL substrate, where usually a sample under test is placed or a microfluidic channel is devised. Therefore, the intrinsic sensitivity of a slot-line dielectric characterization sensor can be much higher than that of a similar microstrip sensor. On that basis, microfluidic sensors based on the variation of transmission phase in microwave slot-lines for biomedical applications have been proposed. Also, different methods for adjusting (decreasing or increasing) the sensitivity of the proposed sensor depending on the application have been studied. Considering the advantages of differential sensors, such as high immunity to noise and ambient conditions, a differential microfluidic sensor based on the same concept has been presented. Finally, a comparison to the state-of-the-art microwave microfluidic sensors with similar principle of operation has been provided.

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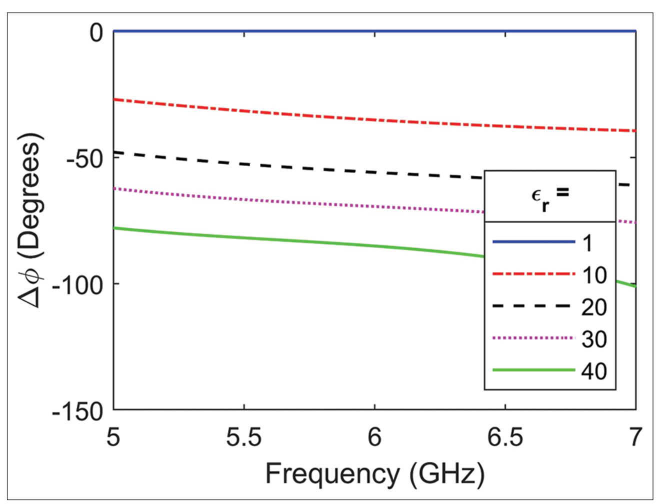

Figure 8: Electromagnetic simulated differential transmission phase $\Delta\phi$ of the differential sensor with respect to a reference empty microfluidic channel (or a liquid under test with a permittivity of ϵ_r = 1)

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Conflicts of interest

There are no conflicts of interest.

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