CONTACT LESS RADIO-FREQUENCIES BIOSENSOR FOR BIOLOGICAL PARAMETERS ANALYSIS

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Abstract: This paper presents a biosensor, which both takes benefits from RF/microwave detection scheme for contactless ability and from microtechnologies fabrication potentialities for massive integration of sensors into lab on chip. The proposed sensor is based on transmission line (which is the basis element of numerous microwave circuits) associated with a biological micro volume in interaction with electrical microwave fields. Thanks to the transmission characteristic of the line, we then detect the presence of DNA inside its nominal liquid environment with a measured sensitivity compatible with RF/microwave measurements capabilities. The results then demonstrated the potentialities of this approach for the analysis of biological parameters of 'in vitro' biological substance using microsystem integration facilities.

1 INTRODUCTION

In the past decades, the biological and medical fields have been strongly modified with the emergence of various bio and micro-sensors for the characterization and quantification of biomolecules. Such sensors permit indeed to reach important parameters for biologists. Classical detection sensors (Bashir, 2004) are very effective, but may sometimes suffer from limitations such as the use of markers, that may modify the studied biological substance. They may also imply high cost and volumic equipments especially with fluorescence, as well as low sensitivity.

To overcome these drawbacks, the use of electromagnetic field as transduction in the bio-sensor may present great advantages. It could provide a non-invasive detection as it is contact less in a biological environment, as well as label free. Some studies have already been performed, notably for toxicology purpose, with the work of Sebastian, 2004 in order to be able to detect heavy metal pollutants in tissues. Some others have focused on the RF field effects on human or livings cells for dosimetry aims (Gabriel, 1996 for example).

In RF measurements, large volume of liquids are usually involved during the characterization to achieve a high sensitivity (Liu, 2008). Thanks to the integration capabilities of microtechnologies, we demonstrate simultaneously high sensitivity (for DNA detection notably) and high compactness, which is compatible with future massive parallel analysis.

Consequently, this paper deals with a very compact RF based bio-sensor, which can serve to detect, identify and quantify very low volumes (few µl) of biological substances. As an example, DNA solution has been chosen as detected solution in order to prove our RF biosensor concept.

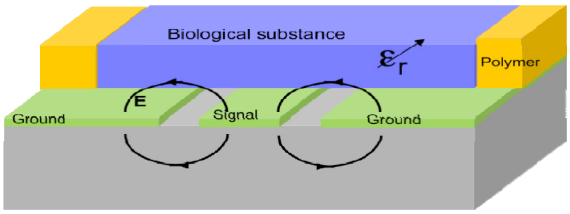

Figure 1: Schematic view of the proposed RF biosensor.

The second part of this publication presents the architecture of our proof of concept demonstrator and describes the validation of the measurement and modeling procedure specifically developed for liquid parameters analysis. The third paragraph deals with the experimental protocol used and measurements obtained for DNA detection inside buffer liquid which highlight the potentialities of our RF/

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microwave based sensor for biological parameters analysis as summarized in the conclusion.

2 RF BIOSENSOR DESCRIPTION

2.1 Device Topology

The investigated RF biosensor is presented in Figure 1. It is composed of a RF transmission line with polymer walls realized on top, in order to delimitate the liquid biological substance area.

A coplanar type of line (a signal path localized between two ground planes) has been chosen, as it permits to elaborate all signal and ground planes on the same surface in one technological step.

Thanks to the polymer walls realized on top of the line, it is possible to characterize various biological substances in an appropriate environment and with very small volume (few µl range). The liquid is inserted on top of the signal thanks to a micropipette and well delimited with the polymer walls.

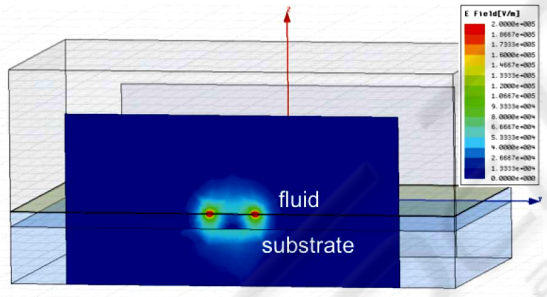

Figure 2: Electrostatic field distribution.

The principle of this biosensor is as follows: the electromagnetic field propagates along the coplanar line. The operating microwave frequency range permits to assure a complete penetration of the field into the biological substance, then enhancing the sensitivity. The fluid presence translates into a modification of the magnitude and phase of the signal as the fluid presents different dielectric characteristics than air. This electrical signature is related to the biological substance properties, and then permits its characterization/ identification/quantification.

The RF biosensor is consequently totally contact less, which avoids any contamination of the chemicals. Labels on the biomolecules are also useless in this case.

Because of the coplanar topology of the line, the electrical field is in consequence almost equally distributed on both side of the line: in the substrate and in the fluid. This phenomenon can easily be noticed in Figure 2.

This permits to get a volumic interaction with the biological substance and furthermore to enhance the sensitivity of detection.

2.2 Calibration Protocol and Validation

Test structures have thus been realized. Gold lines have been deposited on top of a quartz substrate. Polymer walls have then been performed on top to elaborate the fluidic pool. The picture of the obtained demonstrator is indicated in Figure 3.

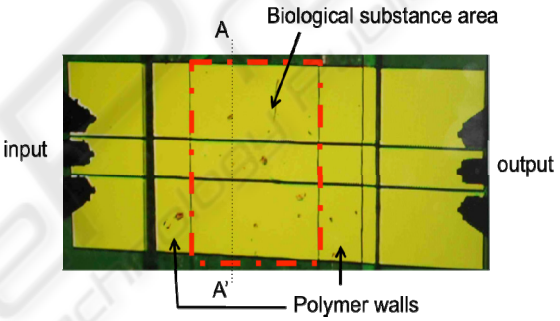

Figure 3: Picture of the RF biosensor with liquid between the polymer walls.

In order to calibrate the extraction procedure of the liquid parameters, we have measured the performance of the proposed test structure with DI water. The Figure 4 presents the extracted permittivity of the DI water (continuous line) and the predicted one (dots) based on the cole-cole theory (Buchner, 1999) (Jiang, 2004). The predicted effective permittivity is computed thanks :

- to the equation 1, which considers that the dielectric field is equally distributed in the water (upper part of the coplanar line) and the quartz material (lower part of the coplanar line).

$$\varepsilon_{r,eff} = \frac{\varepsilon_{r,quartz} + \varepsilon_{r,Water}}{2} \quad (1)$$

- the classical cole-cole equation, described by equation 2, where ε_0, ε_∞ and τ are respectively the permittivity at low frequency, the permittivity at high frequency and the relaxation time.

$$\varepsilon_{r,Water} = \varepsilon_0 + \frac{\varepsilon_\infty - \varepsilon_0}{1 + (\omega \times \tau)^2} \qquad (2)$$

The measured relative permittivity is extracted from the phase of the transmission parameter measured from 100MHz up to 40GHz.

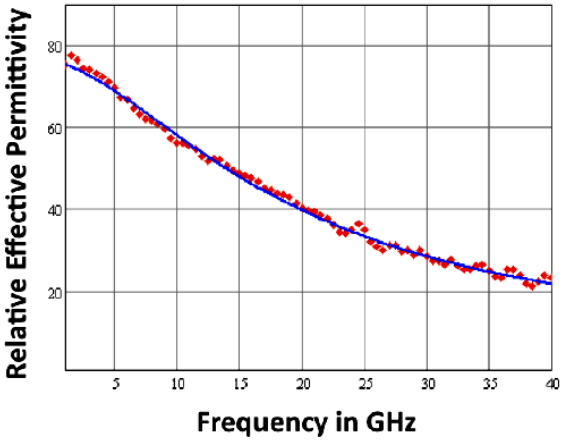

Figure 4: Measured and modeled relative effective permittivity of the test structure.

The good agreement (error lower than 15%) observed between our proposed test structure and the associated extracted procedure with theoretical data taken in the literature then validates our approach over a very broad bandwidth from 100 MHz up to 40GHz.

This validation step then opens the door to the RF and microwave spectroscopy of biological substance given electrical parameters as presented in the next paragraph.

3 EXPERIMENTS AND DISCUSSIONS

Both biological experimental protocol and results are presented in this paragraph.

3.1 Biological Experimental Protocol

In order to perform the RF measurements, two solutions have been prepared and characterized. The first one is directly ready and commercialized for characterization: a λ-DNA solution, which DNA concentration corresponds to 0,37µg/µl. As reference, the buffer solution in which the λ-DNA is localized was also fabricated.

Both liquids have then been tested on our RF biosensor. A micropipette was used to well localize the liquid in the dedicated area, as shown in Figure 5.

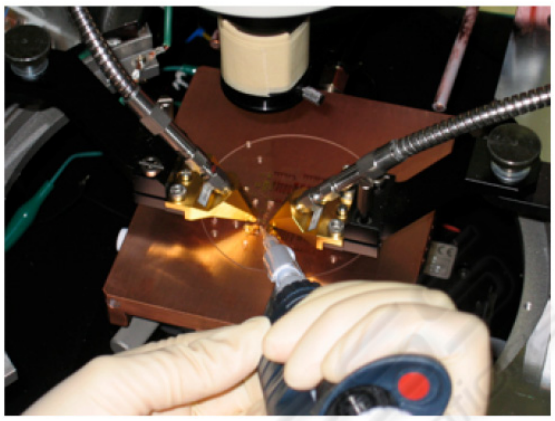

Figure 5: Picture of the RF biosensor under test during DNA solution incorporation with a micropipette.

This figure also presents the RF test setup: two microwave coplanar probes connected to an network analyzer (which operates from 100MHz up to 40GHz) by cables.

We would like to emphasize the fact that our concept is fully compatible with the use of micro-channel.

3.2 Discussions

The electrical parameter, which is monitored, corresponds to the phase of the transmission parameter of the coplanar line. As already reported in this publication, this parameter is related to the permittivity of the biological substance and then to its intrinsic constitution.

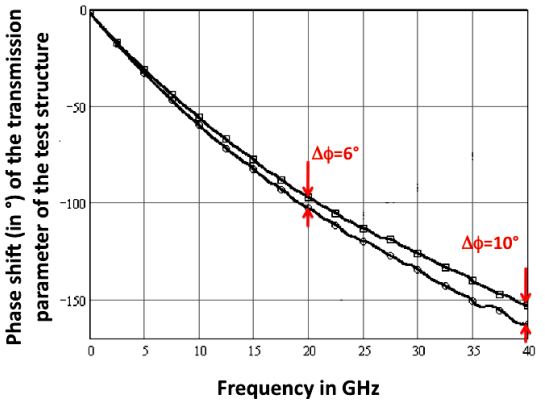

Figure 6: Phase of the transmission parameter vs frequency for the two biological substances: buffer solution w/ (line with circle marks) and w/o (line with square marks) λ-DNA.

The Figure 6 presents the measured phase of the transmission parameters of the tested structure for two cases: (1) when the line is covered with the buffer only (line with square marks) and (2) when the line is covered with DNAs inside the buffer (line with circle marks). As the electrical properties of the DNA molecule differ from the buffer one, we can observe on the RF/microwave measurement the signature of the DNA's loading. We indeed obtain a phase difference of 6° and 10° at 20GHz and 40GHz respectively between the two cases, with and without DNA, as summarized in the table I.

Table 1: Phase measurements summary.

Phase of the transmission parameter in °	20 GHz	40 GHz
Without DNA	-97	-153
With DNA	-103	-163
Difference	6	10

The observed phase difference, around 7% in our case, is larger than the minimum detectable phase shift that we have estimated around 1°, but also sufficiently high to envision microwave circuits with enhanced sensitivity (7% multiply by the order of the electrical function) like filter with operation frequency sensitive to DNA concentration.

We also would like to outline that the use of higher frequency increases the electrical signature (the phase shift in our study) of DNA concentration, and then to highlight one key point of our work, which targets the integration of microwave (1-30GHz) and even millimeterwave (30GHz to 110GHz or even higher) circuit for biological analysis.

4 CONCLUSIONS

This publication presents a proof of concept demonstrator that emphasizes the potentialities of RF/microwave detection and quantification of DNA in its nominal biological environment. We take benefit from the RF/microwave fields to achieve a contact less detection scheme opening the door to 'in vitro' analysis. We have first calibrated/validated our RF sensor, and associated parameters extraction procedure, with known liquid (D.I. water). We have then detected the presence of DNA inside on host liquid with a sensitivity, which is compatible with measurement capabilities and future circuit design of dedicated function.

Besides this electrical characterization, we would like to outline that the fabrication of our sensor is fully compatible with microtechnologies and then inherit of their great interest, notably the possible integration into lab-on-chip.

Furthermore, we think that it will be possible to have access to the intrinsic DNA electrical parameters and density, opening the door to the quantification/discrimination of DNA inside its biological environment.

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