Micro- and millimetre wave measurements of nanolitre biological liquids by dielectric resonators

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***Abstract* — A variety of dielectric resonator techniques from low GHz frequencies towards 100 GHz has been investigated with respect to their suitability for highly accurate dielectric measurements on liquids within microfluidic systems. Whispering gallery type dielectric resonators have been employed for frequencies from 10 to 40 GHz and 2D photonic crystal slab defect resonators for 100 GHz and beyond. Experiments on organic aqueous solutions and cell suspension were analyzed in terms of their potential for label-free biosensor applications.**

***Index Terms* — Dielectric measurements on liquids, organic molecules and cells, whispering gallery dielectric resonators, photonic crystal slab structures**

I. Introduction

The frequency range from about 10 GHz to about 1 THz offers challenging perspectives for label-free and free-solution biosensing. Water, as the most abundant material in the human body, exhibits strong absorption in this range, which can be described by a double Debye relaxation. The challenge for biosensing lies in accurate measurements of alterations of the complex dielectric permittivity of water, as being induced by dissolved or dispersed species and by bound water near the surfaces of proteins. In this context it is of high relevance that the cell membranes are transparent for this frequency range, unlike in the kHz to low GHz range, where the cell membrane relaxation and dissolved ions dominate the response, and unlike in the visible and IR range, where scattering at cells plays a dominant role. Therefore, quite uniquely, the microwave-to-terahertz range provides a new window into the interior of cells. Although being not very specific to certain biomolecules, "global" cell parameters like bulk water, bound water and protein content are complementary to specific biochemical properties which – in conjunction with fast measurements on small volumes within a microfluidic environment – may advance to a new window for medical diagnostics.

Due to the high level of dielectric losses of water, the complex dielectric permittivity of aqueous liquids within microfluidic channels or reservoirs of nano-to-microlitre volume can be determined with high precision by use of a cavity perturbation approach. Considering a resonant mode of unloaded resonant frequency f_0 and quality factor Q_0 , the liquid induced alterations of the resonant parameters, $\Delta f = f - f_0$ and $\Delta Q^{-1} = Q^{-1} - Q_0^{-1}$, can be written as

$$\frac{\Delta f}{f_0} + j\Delta Q^{-1} = \frac{\int_{Vp} E_P{}^2(\vec{x}) d^3x}{2W} \left[\left(\frac{\varepsilon' - 1}{2}\right) + j\varepsilon''\right] \qquad (1)$$

with W denoting the total stored electromagnetic (em) energy, and $\boldsymbol{E}_p(\boldsymbol{x})$ the electric field inside a volume V_p which is perturbed by a liquid sample of complex dielectric permittivity $\varepsilon^* = \varepsilon' + j\varepsilon''$. Eq. 1 presumes that the permittivity does not vary over the volume V_p, which is not always the case. In fact, it is quite common that due to the presence of the liquid the em field is distorted in a volume exceeding that of the liquid. Hence, the integration in Eq. 1 often needs to be extended over parts of the cavity volume which are not filled with the liquid. As a result, the Δf and ΔQ^{-1} dependence on ε' and ε'' may not be separable as indicated by Eq. 1. However, in case of small complex permittivity changes, as e.g. induced by concentration changes due to dispersed microparticles, the assignment of Δf to ε' and ΔQ^{-1} to ε'', respectively, works in many cases, but requires a proper calibration.

For a comparison of the sensitivity of different resonator designs the change of the resonant frequency due to a change in permittivity by one unit (ε_r=2 in Eq. 1), normalized to the unperturbed resonant halfwidth $\Delta f_{1/2}=f_0/Q_0$, represents a meaningful figure-of-merit (FOM). Under the simplifying assumption that the electric field is constant over the volume of the liquid ($V_l \approx V_p$), the FOM for a standardized volume – typically 1 nanolitre - can be written as.

$$FOM = Q_0 \times V_l \times \frac{\varepsilon_0 E^2}{2W} \qquad (2)$$

Commercial em field simulation software can be used to generate plots of the em field distribution normalized to the total electromagnetic energy, for example W = 1J. Hence, the FOM can be easily estimated – in conjunction with a simulated or measured Q_0 value.

Eq. 2 indicates that the highest sensitivity can be achieved by the combination of a high electric field E at the location of the liquid sample and a high quality factor Q_0. Quite often, these criteria are contradictive and each structure needs to be optimized by numerical field simulations.

II. WHISPERING GALLERY MODE RESONATORS

Whispering gallery modes (WGM's) are modes of high azimuthal order (n>6) inside a cylindrically (or spherically) shaped dielectric disks. A high degree of em energy confinement and hence high Q factors can be achieved due to total reflection. In case of placing a microfluidic reservoir close to the surface of the dielectric disk, the evanescent field at the position of the liquid is of the same order of magnitude than the field in the interior of the disk. According the Eq. 2, the FOM can be estimated from the azimuthal mode number n, the permittivity ε_{DR} and the loss tangent tanδ of the dielectric puck material, and the resonant frequency f. It is obvious that the lowest possible mode number, a large value of the puck permittivity and a low loss tangent lead to a high FOM. In Ref. 2 we used a sapphire ($\varepsilon_{DR}\approx 10$) WGM-DR at 35 GHz operated in a mode with n=12, the measured $Q \approx 1/\tan\delta$ was 40,000. According to Eq. 2 the FOM comes out to be 0.7. Fig. 1 from Ref. 1 shows the measured effect of a 1.8 nl droplet of water on the resonance curve (insert) and the measured concentration dependence of organic solutions of (sub) nanolitre sized droplets.

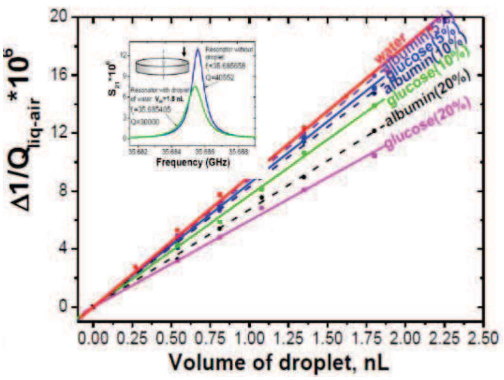

Fig.1: Experimental results of inverse Q change due to (sub)nanolitre droplets of organic aqueous solutions measured by a sapphire WGM resonator at 35 GHz (from Ref. 1).

In Ref. 2 highly accurate measurements of the glucose concentration in water by a sapphire WGM resonator at 10 GHz are reported. In Ref. 3 we describe a ceramic DR of permittivity 28, excited in a low-order WGM of n=6

@10 GHz, the Q was about 10,000. The FOM value of this cavity comes out to be 0.037, still high enough for measurements on sample volumes of less than one microlitre, which is ideal for blood diagnostics.

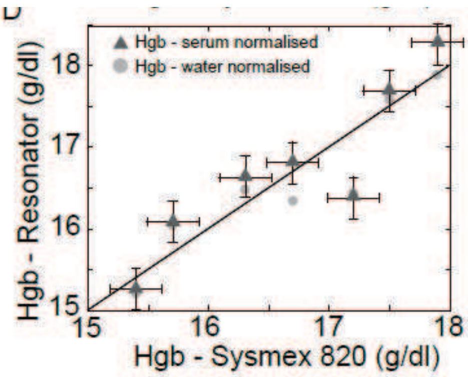

Fig.2: Comparison of a resonator-based determination of the haemoglobin concentration in different blood samples (referenced against the blood serum), in comparison to the gold standard method (Sysmex) (from Ref. 3).

Fig. 2 shows that this system can be calibrated in order to perform accurate haemoglobin concentration measurements in sub-microlitre blood samples – as a minimal invasive tool for anemia diagnostics.

III. INTEGRATED PHOTONIC CRYSTAL DEFECT RESONATORS

For higher frequencies, a concept of a chip-integrated high Q dielectric resonator appears most appealing in order to increase the FOM in a fully integrated system. We have developed and optimized a line defect resonator within a 2D photonic crystal by deep reacting ion beam etching of a thin wafer of high resistive silicon (HRS, $\varepsilon_r \approx 11$) (Ref. 4). For the selected resonance frequency of 100 GHz in the fundamental mode (n=1) and the measured Q factor of about 5,000 the FOM comes out as high as 23. Fig. 3 shows a photograph of the HRS chip-based high-Q defect resonator, which is excited by rectangular waveguide ports via integrated line defect waveguides. The insert shows a 200 micron quartz capillary tube passing through one of the holes of the photonic crystal lattice, the water volume which interacts with the em field is about 1 nl. The resulting measured frequency shift was more than one resonant half width. This technique can be scaled up to a frequency of at least 500 GHz, which would enable accurate measurements of liquid volumes corresponding to a single biological cell.

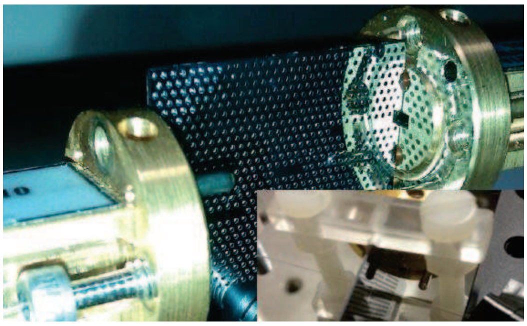

Fig. 2: Photonic crystal slab defect resonator for *f* = 100 GHz, micromachined from HRS, attached to waveguide ports for defect mode excitation. The insert shows a quartz capillary for nanolitre liquid measurements (from Ref. 4).

IV. Conclusion

Whispering gallery mode dielectric resonators were successfully used for concentration measurements of organic molecules dissolved in water and for the assessment of the haemoglobin concentration in blood samples. The ability to perform measurements on small volumes inside microfluidic channels can be expresses by a figure-of-merit, which can be estimated from the simulated em field distribution. For integrated lab-on-chip type dielectric measurements above 100 GHz, 2D photonic crystal slab line defect resonator have a strong potential to enable dielectric measurements in single cells.

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