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proceedings

Abstract

Dielectric Spectroscopy for Non-Invasive Sensing of Multi-Layered Organ-on-Chip Devices †

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Abstract: Organ-on-chip (OoC) is emerging as a key technology for improved pre-clinical drug testing. Monitoring tissues and the artificial microenvironment in OoC devices is critical to recapitulate human physiology; however, sensing is often invasive, superficial, and not continuous over time. This work aims to overcome these issues by proposing dielectric spectroscopy as a non-invasive and time-continuous sensing technique capable of extracting information from multi-layer OoC devices, including distinguishable tissue layers. The presented results set the foundations for this goal by proving this technique's feasibility, showing excellent correspondence between the experimental and modelled data, and providing design guidelines for application-tailored optimization.

Keywords: dielectric spectroscopy; label-free; micro-physiological systems; non-invasive; open-ended coax; organ-on-chip; reflectometer; sensing

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1. Introduction

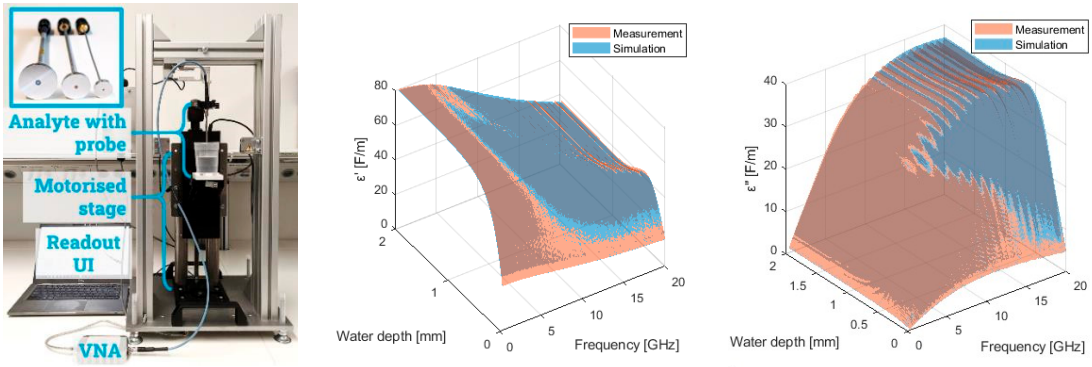
The rising costs and duration of pharmaceutical research and development (R&D) negatively impact the time-to-market for new, affordable, and effective drugs [1]. Over the last decade, organ-on-chip (OoC) technology has emerged to address this issue, aiming to develop accurate in vitro models of human organs. OoC models could be applied in pre-clinical drug testing, aid in personalised medicine, and leverage the ethical burden of animal-based drug studies [2].

To advance time-continuous, non-invasive monitoring—one main unmet need in OoC applications [2]—we propose dielectric spectroscopy (DS) as a sensing technology. The dielectric spectrum depicts a material's response to an electric field across frequencies, which is unique for any given material [3]. Therefore, DS could hypothetically identify specific cell contents and concentrations in media and extract cell properties, such as cell size, permeability, and cell membrane thickness. Furthermore, DS is label-free and non-invasive, making it, in principle, ideal for sensing applications using OoCs. Identifying layer-specific spectral information from the cumulative dielectric response of stacked multi-material layers, as occurs in OoC devices, is central to this endeavour, and hereby, addressed.

2. Materials and Methods

Through our implementation, DS is conducted using a vector network analyser (VNA) connected to a flanged, open-ended coaxial line (Figure 1a) calibrated to the medium's surface using three different reference liquids. The probe can be vertically positioned with micron accuracy using a motorised stage and a load cell (Figure 1a). Using a lookup table-based numerical model, the measured field reflected from the tested medium is converted to a dielectric spectrum [4], which is a method that was verified by comparing with both well-known liquids (independent from those used for calibration) and simulation models.

This work investigates and characterises an expansion of this numerical model, which can extract refined dielectric spectra of multiple stacked material layers instead of just a bulk material spectrum, paving the way for the dielectric spectrum analysis of stratified OoC models.



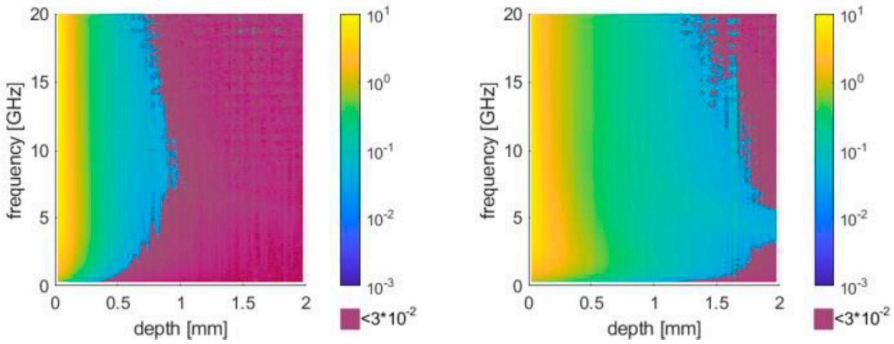
(**a**) (**b**) (**c**)

Figure 1. (**a**) The DS measurement setup. Different probe types are shown in the top left inset. (**b**,**c**), respectively, show the real and imaginary dielectric permittivities for different water depths over glass. Measured data (red surface) overlap excellently with the numerical model prediction (blue surface).

3. Results and Discussion

The model's performance was benchmarked by measuring a multi-layer structure as a single bulk material and comparing the experimental spectrum to that computed by the numerical model. Figure 1b,c shows the smooth transition from the permittivity of water at a depth of 2 mm to that of the glass container at a depth of 0 mm. The data show an excellent match for the full range of heights, with a mean complex permittivity error of 2.42% (σ = 1.35%) over 118,500 datapoints of three differently sized probes. This proves that the numerical model can fully capture experimental data and can be used for multi-layer dielectric permittivity extraction, for which accuracy across depths is essential.

Additionally, we characterized probes of three different diameters (Figure 1a) to test how their dimensions influence sensitivity and the sensing volume (Figure 2a,b), which can be used as a future design guideline.



(**a**) (**b**)

Figure 2. Sensitivity in water over frequency and depth, measured in $\frac{\delta S_{11}}{\delta d}$, where S_{11} is the electric field reflection coefficient, and d the distance between the probe surface and the glass container. (**a**,**b**) show the sensitivity for probe diameters of 0.94 mm and 3.00 mm, respectively.

In our follow-up work, the spectrum extraction of specific layers in stratified samples will be benchmarked. This will consist of three parallel measurements of the same analyte (Figure 3) as follows: a reference in direct contact with the analyte, and two multi-layer

conditions, one with an interposed elastomer (poly-dimethylsiloxane (PDMS)) and one with PDMS and glass. The latter ones are common structural layers in OoC devices, whose characterisation will aid in future non-invasive experiments with tissues.

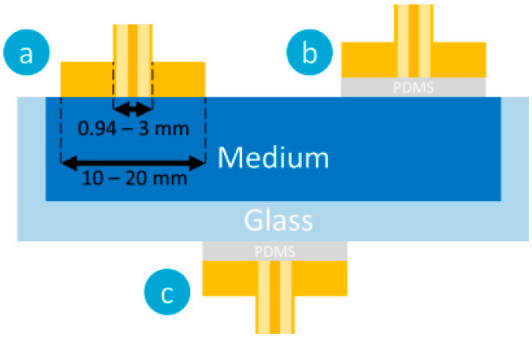


Figure 3. Envisioned measurement setup for benchmarking multi-layer spectrum extraction. (**a**) Uncoated reference; (**b**) two-layer extraction with PDMS interposer; (**c**) three-layer extraction with PDMS and glass.

Author Contributions: Conceptualization, T.H., M.M. and M.S.; methodology, T.H.; software, T.H.; validation, T.H.; formal analysis, T.H.; investigation, T.H.; resources, T.H., M.M. and M.S.; data curation, T.H., M.M. and M.S.; writing—original draft preparation, T.H.; writing—review and editing, T.H., M.M. and M.S.; visualization, T.H.; supervision, M.M. and M.S.; project administration, T.H., M.M. and M.S.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.

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