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METASURFACE DESIGN FOR DETERMINATION OF PROTEIN CONCENTRATION IN ENZYMATIC REACTION MIXTURE

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Abstract *— In the paper a standard multiwell plate structure was utilized to determine the concentration of human serum albumin in water solutions and enzymatic reaction mixtures. This study marks the first application of the multiwell plate structure as a resonant metasurface unit cell through numerical simulation using the COMSOL Multiphysics software. By adjusting the operating parameters of the proposed multiwell plate (MWP) metasurface, resonance phenomena within the microwave range could be observed. The complex permittivity (CP) values of the tested solutions, obtained experimentally using the microwave dielectrometry method, were employed for the MWP metasurface modelling. The correspondence between the resonance frequency shifts of the MWP metasurface and the changes in CP values of the tested solutions was demonstrated. For the convenience of the protein concentration determination, the concentration calibration graph was proposed. Our approach enables the detection of protein concentration in the reaction mixture after 60 minutes duration of the enzymatic reaction course. The study demonstrated the customization of metasurface dimensions to enable interaction with electromagnetic waves at specific frequencies. The availability of standard multiwell plates in different sizes allows for testing solutions across various frequency ranges.*

Keywords*: metasurface, dielectrometry, multiwell plate, microwave, complex permittivity, human serum albumin, enzymatic reaction, trypsin, COMSOL Multiphysics, modelling*

I. INTRODUCTION

The protein concentration determination, in particular determination of the most abundant human blood plasma protein, human serum albumin (HSA), is one of the most requested diagnostic procedures in clinical laboratories. Abnormal HSA concentration indicates various human pathological conditions such as cardiovascular disease, hypertension, renal disease, etc. [1, 2]. For biochemical determination of the quantities of the proteins in human blood samples in biomedical laboratories the numerous variations of multiwell plates, such as the 96-well plate [3] are used. Evaluation of the proteins concentration is important not just for medical diagnostics, but also for a number of technological processes in pharmaceutical and food industries. One of the biotechnological stages of the production of vaccines, medicines and food products is the monitoring of the enzymatic reaction of proteins hydrolysis that includes the accurate quantitative protein determination in the enzymatic reaction mixture [4].

The classical laboratory measurements, including enzyme-linked immunosorbent assay (ELISA) and UV-Vis spectrophotometry method, have been employed to study the enzymatic reaction [5, 6]. This approach has a discrete character: it does not provide

operational control of the protein concentration during the hydrolysis reaction. It requires regular sampling from the reaction zone, which can lead to its contamination [7].

Monitoring the course of enzymatic reactions of protein hydrolysis is important for several reasons. Firstly, it provides insights into the kinetics and mechanisms of the enzymatic process. By tracking the progression of the reaction over time, researchers can understand how enzymes interact with proteins, how fast the hydrolysis occurs, and any intermediate steps involved. This knowledge is valuable for studying enzyme function, designing new enzymes, and optimizing enzymatic processes in various fields such as biotechnology, pharmaceuticals, and food processing [8]. Secondly, monitoring enzymatic reactions of protein hydrolysis allows for the characterization of reaction products. Enzymatic hydrolysis of proteins generates a mixture of peptides and amino acids, which may have different biological activities or industrial applications [9].

Moreover, monitoring enzymatic reactions of protein hydrolysis can be used in diagnostic assays. By monitoring enzymatic reactions, changes in reaction rates or patterns can be observed, providing valuable diagnostic information. For example, altered enzymatic activity in certain cancers [10] or digestive disorders [11] can be detected and monitored through changes in protein hydrolysis.

From the above, it follows that the understanding and real-time characterization of enzymatic reaction progress is crucial for the quantitative monitoring of the analyte in the enzymatic reaction mixtures.

Application of a wide spectrum of physical methods, including radio physical methods for biomedical sensoring provides significant progress in the field of biomedical sensors development. New types of materials and sensing devices based on them called metamaterials [12, 13] and metasurfaces [14], have been proposed. Sensor platforms based on the surface plasmon resonances (SPR) are applied for high sensitive biological and chemical sensing for detection of a number of analytes, including proteins, toxins, drug residues, and chemical contaminants [15, 16]. Plasmonic infrared metamaterials are applied for specific detection of individual biomolecules, such as immunoglobulin G (IgG) and protein A/G, whose resonant response can be accurately obtained due to the vibrational properties of these biomolecules [17]. But during the manufacture and in the working process of SPR metamaterial, technological limitations are associated with fabrication at the nanometer scale and also, metal elements of the metamaterial can be oxidized leading to worsening sensing properties [18].

All-dielectric metasurface-based sensors are very popular because they have negligible Ohmic losses, and they were proposed as alternative material to the metallic plasmonic metamaterials [19, 20]. One of the application areas of the all-dielectric metasurfaces-based sensors is the detection of bioobjects and the quantitative biomolecule determination in the tested samples. In the recent research the authors show that the all-dielectric metasurface with graphene monolayer is more stable, sensitive, and harmless for nucleic acid absorption with the ability to regulate the operating frequency of the biosensor by scaling the dimensions of the all-dielectric meta-atom [21].

We performed a comprehensive study using the developed by our team microwave dielectrometry approach and setup for HSA concentration determination in solutions using the microwave dielectrometry technique and developed experimental setup [22-24]. The microwave range is more suitable for studying samples, the main part of which consists of water. The microwave operating range of biosensors-based measuring system is more applicable for water solutions characterization because the maximum frequency dispersion of the complex permittivity (CP) of water and water solutions is located in microwave spectral range [25].

The main task of the current work is the numerical modelling of the MWP metasurface for determination of HSA concentration in different samples and for examining of the progress of enzymatic reaction of HSA hydrolysis using the CP values of the tested solutions previously obtained by our microwave dielectrometry experiments. Using the multiwell plate structure, we exclude the contact of the

liquid of the samples with metal elements of the metal-dielectric metasurfase, which excludes (in the case of practical usage of such sensing elements), the oxidation of metal elements of the metasurface.

II. MATERIAL AND METHODS

Our previous microwave dielectrometry measurement results showed the practicability of the differential cavity cells for real-time monitoring of the enzymatic reaction of the protein hydrolysis in the reaction mixture [23]. Static concentration measurements of the HSA-water solutions and dynamic measurements of the enzymatic reaction of the HSA hydrolysis, depending on the enzymatic reaction time at 31.82 GHz, were carried out [23]. We use the microwave differential dielectrometry method to determine the CP of water-protein solutions and water-protein with trypsin enzymatic reaction mixtures at room temperature.

The reaction of protein hydrolysis occurs by adding the hydrolytic enzyme trypsin into the water-protein solution. Destruction of the protein by trypsin during the hydrolysis reaction course decreases protein concentration in the reaction mixture. The protein concentration changes as an independent process during the protein hydrolysis reaction. The real-time protein concentration determination in the enzymatic reaction mixture is a significant problem.

Tested samples

In the numerical modelling of the MWP metasurface, we use CP data of such tested solutions: 1) water solutions of the protein HSA with the concentrations of 25, 50 and 100 mg/ml; 2) the reaction mixtures of the protein HSA with concentrations 100 mg/ml and trypsin 1 mg/ml from bovine pancreas. The enzymatic reactions process was monitored within 60 minutes. The CP values of the tested solutions obtained by use the microwave dielectrometry method [22-24]. We use the initial solution of the HSA with concentration of 100 mg/ml for prepare its dilutions and obtained the CP values of these tested solutions for construct the concentrations calibration graph (see Fig. 5 below). Trypsin was used in lyophilized form with the concentration of 1 mg/ml. The studied protein HSA and enzyme trypsin are the medicines produced by the Immunobiological pharmaceutical company "Biopharma" and "Merck", respectively. The CP of the tested solutions was obtained at room temperature of 22±1°C.

The MWP metasurface geometry

The modelling of the design and working parameters of the resonant MWP metasurface operating in the microwave frequency range was carried out. Fig. 1 shows the MWP metasurface geometry: unit cell structure of the multiwell plate, perspective view (a) and top view (b). The COMSOL numerical simulation of the MWP metasurface with the periodic boundary conditions of the unit cell of the multiwell plate for protein concentration determination during the enzymatic reaction of the protein hydrolysis course was carried out. A plane wave is given along the z direction, which is normally directed relative to the MWP metasurface. The boundary conditions are periodic along x and y directions.

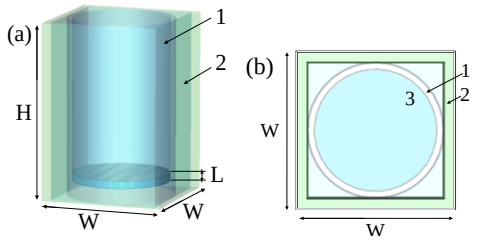

Fig. 1. The MWP metasurface unit cell structure: perspective view (a); top view (b). The numbers correspond: 1 – polycarbonate (ε' =2.9, ε'' =0.01), 2 – polyamide (ε' =3.5, ε'' =0.0027), 3 – the tested liquid layer with the thickness of L

All-dielectric multiwell plate geometry was chosen as the design of the metasurface structure, which does not require manufacturing. The multiwell plate is a standard construction of the 96-well cell for ELISA studies for various laboratory diagnostics. The width, height, and diameter values of the proposed multiwell plate unit cells structure are equal to W = 8.5 mm, H = 12 mm and D = 6.75 mm, respectively.

III. RESULTS AND DISCUSSIONS

A. Optimal operating parameters for MWP metasurface modelling

The selection of operating parameters for modelling a metasurface in the microwave range involves several considerations. Here are a few key factors we considered: 1) Frequency range: determine the desired frequency range for the metasurface application in the microwave frequency range. 2) Resonant behaviour: defined the resonant behaviour required for the

metasurface, such as the desired resonant frequency and the desired response.

Numerical modelling of the MWP metasurface with optimal thickness of the liquid layer L of the tested solutions was carried out. We use the multiwell plate structure implemented as a resonant metasurface unit cell simulation in the microwave ranges. Fig. 2 shows the frequency dependence of the wave reflection S_{11} of the MWP metasurface on thickness liquid layers. We observe that increasing the water layer thickness L leads to the decrease and shift of the resonance frequency of the wave reflection S_{11} of the MWP metasurface.

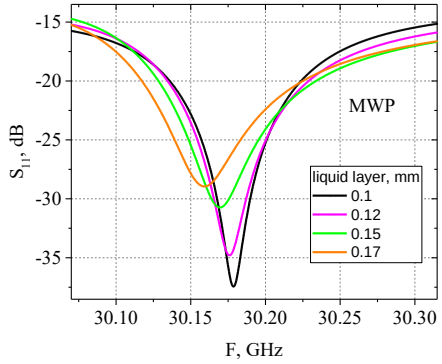

Fig. 2. The wave reflection S_{11} of the MWP metasurface with tested liquid (water) for some thickness liquid layers.

Fig. 3 shows the Q-factor of the resonance frequency S_{11} of the MWP metasurface on thickness liquid layers L as in Fig. 3. With increase of the Q-factor of the resonance frequency it indicates that the metasurface with decreasing the water layer thickness enhances the reflection coefficient of the MWP metasurface. Resonance with a high Q-factor is more desirable when modelling sensors based on the metasurface. The highest Q-factor of the resonance frequency S_{11} observe for the water layer thickness of L = 0.12 mm of the MWP metasurface unit cell. This narrow peak allows for increased sensitivity to changes in the tested solution.

Also Fig. 3 shows the various thickness liquid layers can cause changes the Q-factor value of the resonance frequency of the reflection coefficients S_{11}. The standard multiwell plates come in various sizes, so it is possible to test liquids in various frequency ranges. The observed resonance frequency S_{11} depends on the unit cell size of the multiwell plate. Thus, the resonances will be in different frequency ranges for different standard multiwell plates.

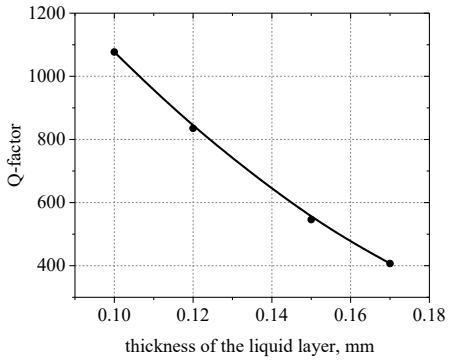

Fig. 3. Dependence of the Q-factor of the resonance frequency S_{11} of the MWP metasurface on the liquid layers thickness.

B. Determination of the HSA concentration in enzymatic reaction mixture

Fig. 4 shows the dependence of the reflection coefficients S_{11} of the MWP metasurface on frequency for water (1), HSA water solutions with the concentration of 25 mg/ml (2) and 100 mg/ml (3) and reaction mixture of HSA water solutions with trypsin (4). A shift of the minimum of the reflection coefficient S_{11} of the MWP metasurface indicates a change in the CP value related to the concentration change of the protein in the solution.

Table 1 shows the CP values for water and HSA-water solutions of different concentrations.

At the end of the enzymatic reaction of protein hydrolysis, estimating the concentration of protein in the reaction mixtures is necessary. We detect the protein concentration changes in the reaction mixture as the resonance frequency shift of the wave reflection of the MWP metasurface. For the convenience of the protein concentration determination, the concentration calibration graph was proposed.

We determine the frequency shift ΔS_{11} of the MWP metasurface due to the changes of the CP values related to the changes of the HSA concentration in tested water solution. Fig. 5 shows the dependence of the resonance frequency shift ΔS_{11} of the wave reflection for the MWP metasurface with the tested solution.

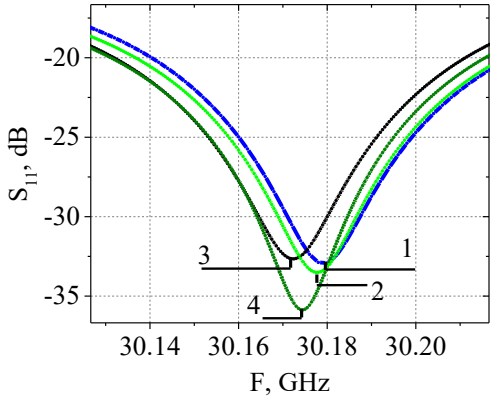

Fig. 4. Frequency dependences of the reflection coefficient S_{11} of the MWP metasurface with water (1), tested liquid for 25 mg/ml (2) and 100 mg/ml (3) concentrations of HSA in water solution and HSA with trypsin in water solution after 60 min. enzymatic reaction time (4).

TABLE 1. The real and imaginary CP parts for water and HSA-water solution on concentration in water solution.

	HSA concentration in water solution, mg/ml	ε'	ε'
1	0 (water)	23.71	31
2	25	20.44	30.93
3	100	18.84	26.93

We have obtained the values of the resonance frequency shift for HSA in water solutions on concentration (Fig. 5, black points). We use this data to construct the calibration concentration graph (Fig. 5, red line – second order polynomial fit) for protein concentration determination during the enzymatic reaction course. The frequency shift ΔS_{11} of the MWP metasurface with protein hydrolysis reaction mixture takes place within 60 minutes (Fig. 5, green triangle). The resonance frequency shift on 4.95 MHz corresponds to the HSA concentration approximately of 60 mg/ml in the reaction mixture (in the case of the HSA concentration before the start of the enzymatic reaction processes is equal to 100 mg/ml) after 60 minutes duration of the enzymatic reaction course. The proposed MWP metasurface makes it possible to detect with high accuracy changes in the concentration in the test solution at small shifts of the resonant frequency ΔS_{11}.

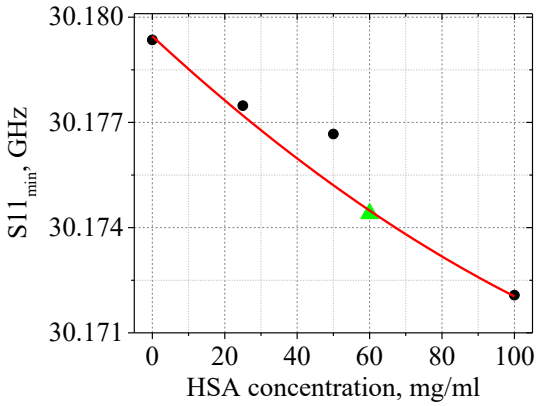

Fig. 5. Dependence of the resonance frequency shift ΔS_{11} of the wave reflection of the MWP metasurface with water and HSA water solution (L =0.12 mm) on the HSA concentration (black point). The green point correspond to the value of the ΔS_{11} resonance frequency shift of the MWP metasurface with located of the enzymatic reaction solution of protein hydrolysis.

IV. CONCLUSION

We demonstrate a novel approach for protein concentration determination during the enzymatic reaction course that combines microwave dielectrometry measurement and the MWP metasurface unit cell numerical modelling. The operating parameters of the proposed metasurface with a tested solution make it possible to observe the resonance of the wave reflection coefficient in the microwave range. Our modelling by COMSOL Multiphysics software revealed the resonance frequency shift of the wave reflection of the MWP metasurface with tested liquid depending on changes of the HSA protein concentration in the tested solutions. The calibration concentration graph is proposed for HSA concentration determinations. It was shown that the dimensions of the metasurface can be tailored to interact with electromagnetic waves at specific frequencies. The standard multiwell

plates are available in various sizes, so it is possible to test solutions in various frequency ranges.

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РОЗРОБКА МЕТАПОВЕРХНІ ДЛЯ ВИЗНАЧЕННЯ КОНЦЕНТРАЦІЇ БІЛКА В ЕНЗИМАТИЧНІЙ РЕАКЦІЙНІЙ СУМІШІ

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Реферат – *У роботі використано стандартну структуру багатолункового планшета для визначення концентрації сироваткового альбуміну людини у водних розчинах та ензиматичних реакційних сумішах. Це дослідження являє собою перше застосування структури багатолункового планшета як резонансної метаповерхневої комірки за допомогою чисельного моделювання з використанням програмного забезпечення COMSOL Multiphysics. Регулюючи робочі параметри запропонованої метаповерхні багатолункового планшета, можна було спостерігати резонансні явища в мікрохвильовому діапазоні. Значення комплексної діелектричної проникності досліджуваних розчинів, отримані експериментально за допомогою методу мікрохвильової діелектрометрії, були використані для моделювання метаповерхні. Продемонстровано відповідність між зсувами резонансної частоти метаповерхні та змінами значень комплексної діелектричної проникності досліджуваних розчинів. Для визначення концентрації білка запропоновано калібрувальний графік концентрації. Наш підхід дозволяє визначати концентрацію білка в реакційній суміші після 60-хвилинного перебігу ензиматичної реакції. Дослідження продемонструвало можливість налаштування розмірів метаповерхні для забезпечення взаємодії з електромагнітними хвилями на певних частотах. Наявність стандартних багатолункових планшетів різних розмірів дозволяє тестувати розчини в різних частотних діапазонах.*

Ключові слова: *метаповерхня, діелектрометрія, багатолунковий планшет, мікрохвильовий, комплексна діелектрична проникність, сироватковий альбумін людини, ензиматична реакція, трипсин, COMSOL Multiphysics, моделювання*