

OPTICAL FIBER BIOSENSORS FOR APPLICATION IN BIOMARKER DETECTION

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DECLARATION

I hereby, declare that this manuscript, entitled “Optical Fiber Biosensors for Application in Biomarker Detection”, is the result of my own work except for quotations and citations which have been duly acknowledged. I also declare that, to the best of my knowledge and belief, it has not been previously or concurrently submitted, in whole or in part, for any other degree or diploma at Nazarbayev University or any other national or international institution.

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Abstract

Currently, there is an increasing demand for fast and accurate analytical methods. Biosensors differ not only in their selectivity, but also in the ability to perform real-time analyses. Biosensors have a biologically recognizing element that can interact only with the target analyte. As a result of the interaction, there is a change in the signal that can be detected. Due to this principle of operation, biosensors have high sensitivity and specificity. Optical Fiber Biosensors are modern and promising methods for detecting biomarkers. This Master Thesis focused on practical experiments and analysis of the detection results of Semi Distributed Interferometers. Experiments were conducted with Alpha-synuclein (phospho S129) peptide. The bioreceptor used for detection was Anti-alpha-synuclein (phosphoS129) antibody. As a result, the value of the Limit of Detection was 415.64 pg/ml, which is not a clinical standard, but has serious prospects for further development. This work also examines another type of biomarker, the steroid hormone progesterone. The detection of the hormone progesterone took place in a solution of Prolutex, which creates additional challenges for the operability of the Optical Fiber Biosensor. The GQ-5 aptamer was used as a bioreceptor for progesterone detection, which in the early work of scientists showed excellent results for electrochemical biosensors.

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List of Abbreviations

OFB	Optical Fiber Biosensor
SDI	Semi Distributed Interferometer
IVF	In-Vitro Fertilization
SMF	Single Mode Fiber
EBF	Enhanced Backscattering Fiber
APTMS	(3-Aminopropyl)trimethoxysilane
PMMA	Poly(methyl methacrylate)
GA	Glutaraldehyde
P4	Progesterone
SG	Savitsky-Golay
LOD	Limit of Detection
FBG	Fiber Bragg grating

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Chapter 1

Introduction

1.1 Optical Fiber Biosensors

Biosensors are widely used in various fields: for example, a glucose meter for measuring blood sugar, and in environmental monitoring, biosensors detect toxins in water or heavy metals in the air. The relevance of biosensors lies in the possibility of rapid analysis and the compactness of the device [1]. Biosensors are a broad class of devices where optical biosensors occupy a special place. Optical biosensors use refractive indices or changes in the spectrum to determine the concentration of biomarkers. The field of application of such sensors is extensive, but the most common is the field of medicine. Optical fiber biosensor (OFB) is used to detect cancer markers, proteins, glucose, and even hormones. OFB is characterized by high specificity, resistance to electromagnetic interference, the ability to combine with portable devices, as well as with detection limits of the target analyte in femtomolar concentrations. This type of biosensors also has prospects for in vivo monitoring, which makes it a universal and promising platform for detecting biomarkers in medicine [2].

1.2 Semi-Distributed Interferometers

Optical fiber biosensors are actively being studied and researched to detect biomolecules. Interferometers are a special highly sensitive group of optical fiber biosensors [1]. Considerable attention is paid to interferometric systems due to their ability to provide high sensitivity to changes in environmental parameters. Semi-distributed interferometers (SDI) are one of the most promising areas for study. In this work, SDI type optical fiber biosensors were used. The principle of operation of SDI is based on the interference of waves propagating in an

optical fiber [12,13]. SDI sensors are highly sensitive to changes in environmental parameters. Even small changes in the interference pattern in the sensitive part of the sensor can be registered by the integration system. Due to their high sensitivity, such sensors can be used to detect various biomolecules such as proteins and hormones [14].

The fabrication SDI type of OFB takes a small amount of time [12], which makes this approach promising in the development of highly sensitive systems. The principle of operation of the SDI is based on the interference of light waves. The interference pattern is created by reflecting the signal inside the sensor structure. The sensitive area of SDI is the tip, therefore, there is no need for large volumes of the sample, a small drop is sufficient [13-16]. Real-time monitoring and the compactness of the systems make SDI a convenient option for biomedical research. To register the signal during the analysis, interrogation devices are used, which provide parameter measurements. Figure 1 shows the schematic of SDI optical fiber biosensor system.

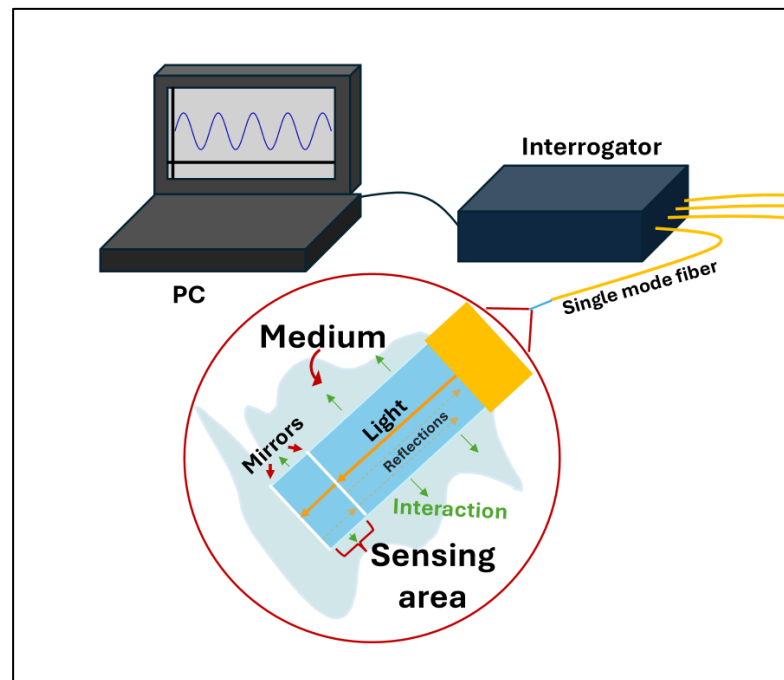


Figure 1.1: Schematical representation of Optical Fiber Biosensor system

Figure 1.1 shows a personal computer (PC) that reads the spectrum registration from an interrogator. SDI type of OFB is connected to the interrogator. The interaction of the tip of the sensor, the sensory part, with the medium has also been demonstrated.

1.3 Alpha-Synuclein and Progesterone as Biomarkers

Certain biomarkers may change due to certain physiological or pathological processes in the body [19]. Changes in the parameters of certain biomarkers may indicate the development of the disease. Among such biomarkers, proteins and hormones are of particular interest. In this project, the protein alpha-synuclein and the hormone progesterone were used as detectable biomarkers. Alpha-synuclein protein and progesterone hormone are important biomarkers and are widely studied in the context of medical diagnostics.

Alpha-synuclein protein is mainly present in the nervous system and is an important biomarker associated with neurodegenerative diseases. Elevated levels of this protein may indicate the development of diseases such as Parkinson's disease, Alzheimer's disease, and dementia [20]. The possibility of early detection of alpha-synuclein can contribute to the diagnosis and timely treatment of the onset of neurodegenerative processes [21]. Thus, the development of highly sensitive biosensors for alpha-synuclein detection will help to cope with the task of timely diagnosis.

The hormone progesterone affects the human reproductive system. Progesterone is a steroid hormone. In women, progesterone is involved in such processes as regulating the menstrual cycle, maintaining pregnancy, and preparing the endometrium for implantation of a fertilized egg. It is especially important to control the level of the hormone progesterone during In-Vitro Fertilization (IVF) [32]. The readiness of the endometrium for the implantation of a fertilized egg can be determined by measuring the progesterone level. If progesterone level is

too high or too low, it can negatively affect the results of IVF. Optical fiber biosensors have the potential to be a valuable tool for the diagnosis of progesterone in reproductive medicine.

In order to detect biomarkers, it is necessary to functionalize the sensor surface with special bioreceptors such as aptamers or antibodies [1,2]. Aptamers and antibodies are able to specifically bind to the target analyte, providing selectivity. Biomolecular binding leads to changes in optical parameters such as refractive index, which can be detected. Figure 2 represents schematical representation of optical fiber biosensor with the functionalized surface.

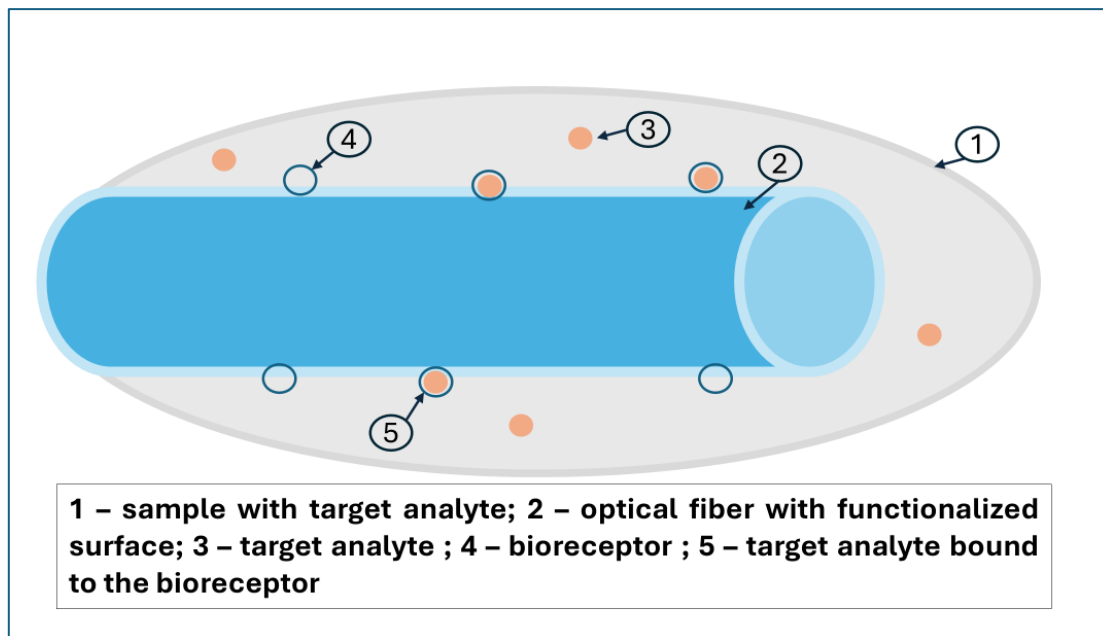


Figure 1.2: Schematical representation of the Optical Fiber Biosensor with functionalized surface

1.4 Research Objectives

Objectives:

1. Create an optical fiber biosensor for detecting biomarkers;
2. Calibrate biosensors. And choose ones with a sensitivity of more than $100 \text{ } d\beta/\text{RIU}$ for experiments;

3. Perform functionalization and detection of target analytes;
4. Collect spectral data depending on concentrations;
5. Create a program for automation of spectrum analysis.

1.5 Research Motivation

Modern methods of biomarker detection incur high monetary and time costs. The requirement of qualified personnel to perform the tests confirms the impossibility of analysis at home. The study of alternative detection methods can facilitate the monitoring of biomarkers and contribute to the early diagnosis of diseases. This project is aimed at the study of Semi-distributed optical fiber biosensors. During this study, various methods of sensor surface functionalization were used, as well as experiments with various types of target analyte.

In this study, two types of target analytes were used: alpha-synuclein protein and progesterone hormone. Alpha-synuclein is a biomarker for Parkinson's, Alzheimer's and dementia diseases. Investigating new methods for detecting this protein could significantly improve the chances of an early diagnosis of neurodegenerative disorders. Experiments were conducted with another target analyte, progesterone, a steroid hormone that plays an important role in women's reproductive health. Progesterone helps regulate the menstrual cycle and supports pregnancy, and its levels need to be monitored during in vitro fertilization (IVF) treatment. If progesterone levels are too high or low, it can lead to miscarriage. The study of methods for detecting progesterone in the context of IVF has the potential to significantly improve monitoring of progesterone levels and increase the chances of successful pregnancy and fetal survival.

The development and research of modern detection methods is of considerable practical interest. Currently, there is a need for alternative analysis methods that are not only highly accurate, but also inexpensive. Optical fiber biosensors offer a promising solution. They

combine high sensitivity and selectivity with low cost, making them a valuable tool for biomolecular analysis. The development of these sensors has led to significant improvements in analytical techniques.

Chapter 2

Literature Review

2.1 Optical Fiber Sensors

Optical fiber can make the measurement of physical, chemical and biological parameters based on changes in the characteristics of light under the influence of external factors [1,2]. Changes in the characteristics of light can manifest themselves in a phase shift of the wave, a shift in wavelength, a change in light intensity. Optical fiber sensors have many advantages; such devices have compact dimensions and high sensitivity. Such sensors can be integrated into various systems, as well as the possibility of remote detection due to minimal fiber losses. Optical fiber sensors are widely used in industry, environmental and biomedical research [3].

The possibility of modifying the surface of optical fiber sensors makes it possible to use them for the detection of biomolecules as biosensors. Optical fiber biosensors are currently being actively researched [4]. To be able to detect a specific biomarker, the sensor surface must be functionalized with bioreceptors. Bioreceptors, such as antibodies or aptamers, bind to the target analyte and ensure the selectivity of the biosensor surface [5]. The specific binding of the molecules allows the sensors to respond only to targeted analytes. This approach reduces the risk of non-specific binding of foreign substances and improves measurement accuracy [6].

Binding of the bioreceptor immobilized on the sensor surface to the target analyte in the sample changes optical parameters such as refractive index and signal intensity. These changes occur in the sensitive part of the sensor and are recorded using the interrogation system. Interrogation systems allow you to analyze spectral characteristics, such as wavelength shifts or changes in the interference spectrum.

In this work, the MATLAB code [1] used for the analysis was improved to analyze the detection data. The code has an identical structure, but there are a couple of differences. In this work, the Savitsky-Golay filter [7] was used, not Butterworth [8]. The Butterworth frequency response is described in formula (1)[8]:

$$|H(\omega)|^2 = 1/(1 + (\omega/\omega_c)^{2n}), \quad (1)$$

In equation (1), ω - is the frequency of the signal, and ω_c - is the cutoff frequency, n - is the filter order. The filter requires cropping the initial points of the spectral data, as it creates a transient at the beginning of the processed signal.

The advantage of Savitsky-Golay is noise reduction, while maintaining the shape of spectral peaks and troughs [7,9]. In the article by Shang Y. et al. [9] demonstrated the use of the SG filter in optical fiber systems. The authors have successfully applied a filter for FBG. The author's algorithm preserved details from excessive smoothing, suppressed white and pink noise. In order to evaluate the operation of the Savitsky-Golay filter, a comparative characteristic was performed with other digital filters [10]. The authors Elgaud M. et al. [10] compared the Savitsky-Golay filter with the Moving Average and the Moving Median filter. The goal was to improve the Time-division Multiplexing FBG. The authors used the SNR (2) metric to compare filters.

$$SNR = 20 \lg \left(\frac{A_{peak}}{A_{noise}} \right), \quad (2)$$

In formula (2), A_{peak} - is the amplitude of the reflection peak, and A_{noise} - is the standard deviation of the noise amplitude. The Savitsky-Golay filter showed a $3d\beta$

improvement in SNR, although it was the lowest result, but it was this filter that did not distort the waveform and retained the pulse shape.

The Savitsky-Golay (SG) filter is indeed an effective tool for spectrum analysis. Peide Liu et al. [11] warned in their work that SG without EMD decomposition causes broadening of the reflection peak, EMD involves decomposition into IMF, equation (3) is presented below:

$$x(t) = \sum_{i=1}^n c_{xi} + r_x(t), \quad (3)$$

However, EMD decomposition will not be used to analyze the detection spectrum of this master thesis, since it is necessary to monitor the change in intensity, not the position of peaks and troughs in the spectrum. Savitsky-Golay equation (4) without EMD [11]:

$$S_{filter(n)} = \sum_{j=-m}^m c_j \cdot S(n+j), \quad (4)$$

A window of $2m+1$ around point n is taken, each point is multiplied by the coefficient c_j and summed. The coefficient c_j depends on the value of the window $2m+1$ and the polynomial.

Since the detection in this study is based on [1], the reference spectrum was calculated using formula (5) [1]:

$$S_{ref} = \left(\frac{1}{N_{measurement}} \right) \cdot \sum_{j=1}^{N_{measurement}} S_{SDI}, j(\lambda), \quad (5)$$

According to formula (5), the peaks were determined by the value of S_{ref} and the valleys by the value of $-S_{ref}$. The mean value and standard deviation were determined by formulas (6) and (7), respectively [1]:

$$\mu_i = 1/N_{measurement} \cdot \sum_{j \in i}^{N_{measurement}} I_k(j), \quad (6)$$

$$\sigma_i = \sqrt{\frac{1}{(N_{measurement}-1)} \cdot \sum_{j \in i}^{N_{measurement}} (I_k(j) - \mu_i)^2}, \quad (7)$$

The assessment of the limit of detection (LOD) is also based on the work of Tosi et al [1]. Since all the studies were conducted in buffer, the formula for normalizing the response is presented in equation (8) [1]:

$$\Delta A_i = \mu_i - \mu_1, \quad (8)$$

The first concentration is always in the buffer without the added target analyte, so this concentration is excluded in equation (8). Linear regression was determined based on equation (9) [1]:

$$A = a \cdot C + b, \quad (9)$$

From equation (9), the value of a - is the slope, C - is the concentration, and b - is set by the condition. The coefficient of determination was calculated by equation (10) [1]:

$$R^2 = 1 - \frac{\sum (y_i - \bar{y}_i)^2}{\sum (y_i - \bar{y})^2}, \quad (10)$$

The weights were calculated according to equation (11) [1]:

$$w_i = \frac{1}{\sigma_i^2}, \quad (11)$$

The weight value is inversely proportional to the value of the square of the standard deviation. The LOD values were calculated using equations (12) and (13) [1]:

$$LOD_y = 3 \cdot \sigma_{max}, \quad (12)$$

$$LOD_x = (LOD_y - b)/a. \quad (13)$$

Based on equations (12, 13), the detection limit can be determined. By the value of the detection limit, it is possible to find out what the minimum amount of the target analyte in the solution can be reliably detected. LOD_y is expressed in units of signal, and LOD_x is expressed in units of concentration.

2.2 Semi-Distributed Interferometers

Semi-Distributed Interferometers (SDI) principles of operation are presented in the article [12]. The authors of the work demonstrated that the creation time of such a sensor takes about 1 minute. To fabricate a sensor, it's necessary to splice 2 types of optical fiber and make a smooth cut. The first type of fiber is Single Mode Fiber (SMF), the second fiber that is used to fabricate the sensor is Enhanced Backscattering Fiber (EBF). EBF has nanoparticles that act as random reflectors. Due to the presence of nanoparticles, the spectrum is obtained with sharp peaks and valleys. After splicing these two fibers, a Fabry-Perrot interferometer is created at the end [12, 13]. Peaks and valleys of the spectrum of such a sensor that have the highest Refractive Index (RI) values. As the data show, valleys are more sensitive than peaks [12, 14]. The maximum sensitivity value of such a sensor is 787 d β /RIU.

An example of using an SDI sensor type is presented in [13]. The authors created a sensor that is specific to three virus proteins. The sensor showed a significant response to the target analytes: virus proteins. The sensors were also analyzed for negative control, and the sensors that did not have immobilized antibodies did not respond. The work has made significant contributions to the development of the SDI sensor type as a device for public health. The SDI sensor type not only shows excellent detection performance, but it is also a cheap tool for detecting targeted biomarkers. In [14], the task of the authors was to detect the chemokine CCL5. CCL5 is the main biomarker of some types of cancer. Although in this work, unlike Adbossova [13], sensors with an average sensitivity value lower were used, but they showed a good response in a buffer with a LOD 2.86 fM. Even in an environment like human serum, the sensor did an excellent job of detecting the target and showed LOD 17.6 aM. The specificity analysis was performed using IL-4 protein and thrombin, the sensor showed minor changes, therefore it was tested for selectivity.

The SDI type of sensor is actively tested not only in a buffer or artificial liquids [14], but also on real samples [15]. In the work of Seitzkamal et al. [15] studies have been conducted to detect the biomarker of renal insufficiency KIM-1. Experiments were conducted, among other things, on real clinical urine samples. As a result, a label-free biosensor was developed that is applicable in point-of-care diagnostics. The estimated cost of such a sensor was also presented in the article, it was approximately 1 USD. The SDI type of sensors has potentially high prospects in the future as a solution for cheap, fast and timely diagnosis of biomarkers [16, 17].

2.3 Alpha-Synuclein Detection

Alpha-synuclein is a marker of Parkinson's disease [18]. Existing traditional methods of analysis are ineffective for operational monitoring of human health, and in some cases, it is possible to examine the brain and confirm neurodegenerative diseases only postmortem [19]. Currently, electrochemical sensors are a large group of modern methods of analysis [20]. But fiber-optic biosensors are an actively developing and promising method.

The first detection of alpha-synuclein by a fiber-optic biosensor is presented in [21]. The authors created a U-shaped fiber-optic sensor with the method of detecting alpha-synuclein Localized Surface Plasmon Resonance (LSPR) fibrils. Anti-amyloid fibrils OC antibody was used to immobilize the sensors on the surface, but these antibodies are not specific specifically to alpha-synuclein, they are bound to fibrils. As a result, LOD 70nM was obtained, according to the authors, this is preliminary data. Later, the authors Khatri et al [5] published an article [22] where they improved the approach, their method made it possible to distinguish between the monomeric and fibrillar forms of the sample. The authors of [23] also created an optical fiber sensor with the LSPR detection method. In this article, the LOD value is 10nM, and measurements were also carried out using the colorimetric method in saliva. Giarola et al [24]

created optical biosensor based on SPR. In their article, the PSMa3 peptide was used instead of the antibody. This peptide binds to toxic alpha synuclein oligomers. The peptide was used instead of other bioreceptors because it has specificity to oligomeric forms and does not bind to monomeric ones. This approach solves the problem of traditional ELISA analysis, because the use of antibodies leads to binding to the monomeric form of alpha-synuclein. In this study, a peptide is also used for the master thesis.

For sensor silanization, APTMS is used by the standard method, but in this work experiments were also conducted with the m-peg: silane-amine silanization method. This method not only increased the sensor response but also shortened the functionalization time. The authors of Hynninen et al [25] performed surface silanization using heterobifunctional silane-polyethylene glycol. The advantages of this method are that such a layer can be applied very thinly, and such a layer has a high opacity, which minimizes non-specific binding. Maldonado et al [26] used *Silane-Peg-COOH* for surface silanization in their work on optical Bimode Waveguide Interferometers (BiMW). The authors obtained a dense layer that is covalently bonded to the surface. It was also noted that such a layer reduces non-specific binding. And the modification of *SiOH* glass using PEG in the work of Seongbong Jo, Kinam Park et al [27] showed that during hydration, PEG chains swell and completely cover the surface. Their experiment was evaluated using XPS and ACM methods. The work of Sadhana Sharma et al [28] also used PEG to create antifouling coatings. The authors used PEG and silicon tetrachloride. Next, the resulting PEG- $OSiCl_3$ was coupled to silicon in toluene. Toluene was previously made anhydrous. As a result, according to XPS estimates, it was found that it is possible to create films with a controlled thickness, PEG coatings reduce fibrinogen adsorption.

Semiconductor materials can be used in modern biosensor functionalization methods. In [45], the authors used a zinc oxide layer as a functional layer. The surface of the sensor, modified with zinc oxide, became not only ideal for immobilizing the bioreceptor, but also

increased the sensor area, which helped to increase the signal. The authors of [46] used semiconductor material for their optical fiber sensor to create a surface for the adsorption of water molecules, thereby changing the sensitivity of the sensor. For some experiments with alpha-synuclein, perovskite was used as a signal amplifier. Perovskite is a semiconductor that is widely used to create photovoltaic devices. There are different types of perovskites: organic, inorganic, hybrid [47]. Recently, perovskite has shown not only high efficiency, but also high performance in terms of its properties, such as high mobility of charge carriers [48]. Perovskite can be used not only as a material for functionalization, but also as a sensitive element. In [29], the authors used perovskite as a sensor functionalization for tetracycline detection, as a result, the authors obtained a sensor with high sensitivity; to protect the sensor from decomposition in water, the authors protected the perovskite layer with a layer of SiO_3 . Various methods can be used to create perovskite. For example, the hybrid type of perovskite is very popular in use, it consists of organic and inorganic materials [42].

2.4 Progesterone Detection

Progesterone detection is necessary not only for humans, but also for the environment for public health [30]. Progesterone is usually a necessary analysis of women's health, as it is produced in the ovaries. During pregnancy, progesterone is also synthesized by the placenta. Progesterone levels affect the mental and emotional state of women [31]. It is worth noting that progesterone is also synthesized in the adrenal glands, brain and other human tissues [32].

In this part of the literature review, studies of various types of biosensors that have been successfully used to detect progesterone will be considered. To find a suitable method and bioreceptor, articles were studied where progesterone was detected using biosensors. Daems et al [33], the authors of the article created a biosensor based on optical fiber and used the Surface Plasmon resonance (SPR) method to detect progesterone. In their case, progesterone was

immobilized on the surface of the sensor, sewn to bovine serum albumin P4-BSA. The interest of this work lies in the fact that the signal will be weak during normal binding, the authors have amplified the signal with gold nanoparticles. The authors also conducted a competitive inhibition assay, since progesterone is a small molecule. That is, the sample not only had progesterone, but also an antibody was added to the sample. Next, the antibody binds to progesterone. After that, a sensor is placed in the sample. Free antibodies bind to P4-BSA, then gold nanoparticles are added to them for SPR analysis. And the more binding occurred on the surface of the sensor, the less progesterone was in the sample. In the work of Zhu et al. [34] the authors also used antibodies for analysis, but they carried out sandwich assay. This is possible because they used not only an antibody, but also an aptamer for binding with progesterone. The antibody and aptamer were connected to different progesterone sites. The aim of the authors was to develop a photoelectrochemical biosensor, where the antibody is immobilized on an electrode, and the aptamer is conjugated with photoactive particles. An aptamer was needed in this analysis to increase the photocurrent signal.

In this work, aptamers for binding with progesterone in solution were used. Therefore, special attention was paid to working with aptasensors. In the work of Jiménez et al. [35] DNA chains that specifically bind to progesterone were found by SELEX. After the ssDNA aptamer was found, 5 clones were isolated: P4G13, P4G11, P4G04, P4G03, P4G06. The highest affinity scores were in the experiments with P4G13 aptamer. The authors revealed this through several stages of experiments. The first stage was determined by the following methods: fluorescent and electrochemical. In the fluorescent method, they labeled FITC fluorophore aptamers. The electrochemical method (EIS) showed the value of the R_{ct} change – a change in charge transfer resistance. P4G13 had the lowest K_d value in both methods. In the second stage, the authors measured how much the structure of the aptamer changes during CD spectroscopy and measured the conformational shift. When interacting with the target analyte, the structure of the

aptamer should change. The most changes were in P4G13 aptamer. As a result, P4G13 was used for specificity analysis by fluorescence analysis, where P4G13 showed very low binding to negative controls: Norethisterone (NET), 17 β -Estradiol (E2). Next, P4G13 was modified with cDNA, in which case the aptamer was used for immobilization on an impedimetric biosensor. The Sun et al review [36] also mentions an article by Jiménez et al. as an example, single biomaterials. The competitor for the P4G13 aptamer is the GQ5 aptamer [37]. The GQ5 aptamer has a G-quadruplex structure, unlike the P4G13 aptamer, and surpasses it in a number of characteristics. GQ5 has a lower K_d value by almost 3 times. Also, the GQ5 aptamer survives not only in the buffer, but also in milk and serum, which is an important indicator, while P4G13 is able to bind to progesterone only in the buffer, and completely degrades in serum. The GQ5 also works even at low concentrations, which the P4G13 could not handle. This comparison is fair, since both sensors were impedimetric aptasensors, for EIS was a gold electrode, therefore there were similar approaches.

Modified aptamers can be used to create an aptasensor. The authors Zeiden et al. [38] used X-aptamers (X-aptamer#3, X-aptamer#4, X-aptamer#5) in their work, these aptamers were modified. In such aptamers, some nucleotides carry amino acids. Since these aptamers are modified and an aptamer has been immobilized on the sensor surface, it is possible to perform a sandwich assay, unlike the work of Daems et al [33], where a competitive analysis was performed with the immobilization of P4-BSA on the sensor surface. The type of progesterone detection is the SPRi method.

Based on the review by Sun et al [36], a significant number of biosensors for progesterone are electrochemical. The review also indicates that along with electrochemical sensors, optical sensors are also actively developing [33,38]. The review article by Altalbawy et al [39] shows the advantages of aptasensors, primarily their specificity, since chains of aptamers are purposefully derived for binding with a specific analyte. Chemical synthesis can

also be used to synthesize aptamers without experimenting with animals, which makes the process more humane. And comparing with antibodies, the use of aptamers is more advantageous in price. The use of aptamers for other types of sensors such as the optical fiber biosensor SDI is a new development, in the modern world there is a need for new developments for the detection of progesterone, which can cover a wider range than electrochemical sensors [40]. Table 2.1 shows an affinity analysis and detection limit, but only for articles with aptamers, since in this study it was decided to choose aptamers for their specificity and cost for the work of master thesis. The tables show the limit of detection values only in the buffer, since in the experimental part of the thesis, detection will also be in the buffer.

Table 2.1 Aptamers characteristics

Aptamer	Biosensor	K_d	LOD	Ref.
1	2	3	4	5
PG13 aptamer	Impedimetric Biosensor	16.81 ± 3.12 nM	0.90 ng/mL (dynamic range: 10 to 60 ng/ml) in phosphate buffer	[35]
GQ5 aptamer	Impedimetric Biosensor	5.29 ± 2.9 nM	0.53 ng/ml (dynamic range: 0.1 to 50 ng/ml) in spiked buffer	[37]
X-aptamer#3	Optical Biosensor	21.74 pM	-	[38]
X-aptamer#4		28.10 pM	1.575 ng/ml (dynamic range of 1.575 to 126 μ g/ml) in phosphate buffer	[38]

1	2	3	4	5
X-aptamer#5		25.58 pM	1.575 ng/ml (dynamic range of 1.575 to 126 µg/ml) in phosphate buffer	[38]

The aptamer Kumar et al [37] will be used in this master thesis. Since the sensor to be used is an SDI optical fiber biosensor, the principle of sensor functionalization with an aptamer will be used from the article by Bekmurzayeva et al. [41]. The authors detected thrombin in the range from 10nM to 80nM. The main criterion for evaluating detection was the wavelength shift, the dependence was almost linear – the higher the concentration, the stronger the shift.

Chapter 3

Methodology

3.1 Principle of Fabrication of Semi-Distributed Interferometers

In this work, SDI type OFB was used. To fabricate SDI, two types of fiber must be used. A single-mode fiber (SMF) with an FC/APC connector, such a fiber with a connector is called a “pigtail”. And the second is Enhanced Backscattering Fiber (EBF). EBF has nanoparticles, this fiber is doped with magnesia silicate nanoparticles. We will also need a Hole Fiber Optic Stripper, clips/holder, glue, lint-free wipes (if necessary), and a fiber welding machine (fusion splicer) for the sensor. The necessary tools for fabrication are shown in Figure 3.1.

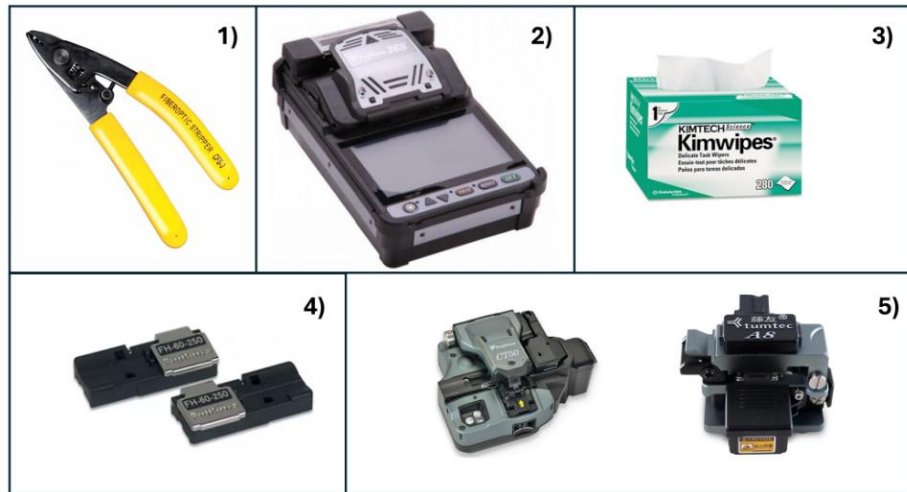


Figure 3.1: All necessary tools for fabrication SDI type sensor: 1) Hole Fiber Optic Stripper; 2) Fusion splicer Fujikura; 3) Lint-free wipes (Kimwipes); 4) Holders; 5) Cleaver: Fujikura CT50, Tumtec A8

The principle of SDI sensor fabrication is simple. It is necessary to prepare two types of fiber SMF and EBF [12]. Then remove the insulation area and the cladding from the SMF and remove the cladding from the EBF. A Hole Fiber Optic Stripper was used for removing, for EBF it is necessary to use special clips/holders to fix the fiber during cleaning so as not to damage it [14].

After preparing the fibers, they must be spliced together. Before soldering, a smooth cut is made to minimize losses during soldering. The cut can be made using a cleaver. We make smooth cuts on two types of fibers, if necessary, the fiber can be wiped with lint-free napkins to remove pieces of cladding or stuck particles. Then two fibers should be soldered using a Fujikura fusion splicer. Next, it's necessary to take out the soldered fiber and make a cut so that about 1 mm remains from the part with EBF [16]. Figure 3.2 shows the structure of the sensor creation after the preparation of the SMF and EBF.

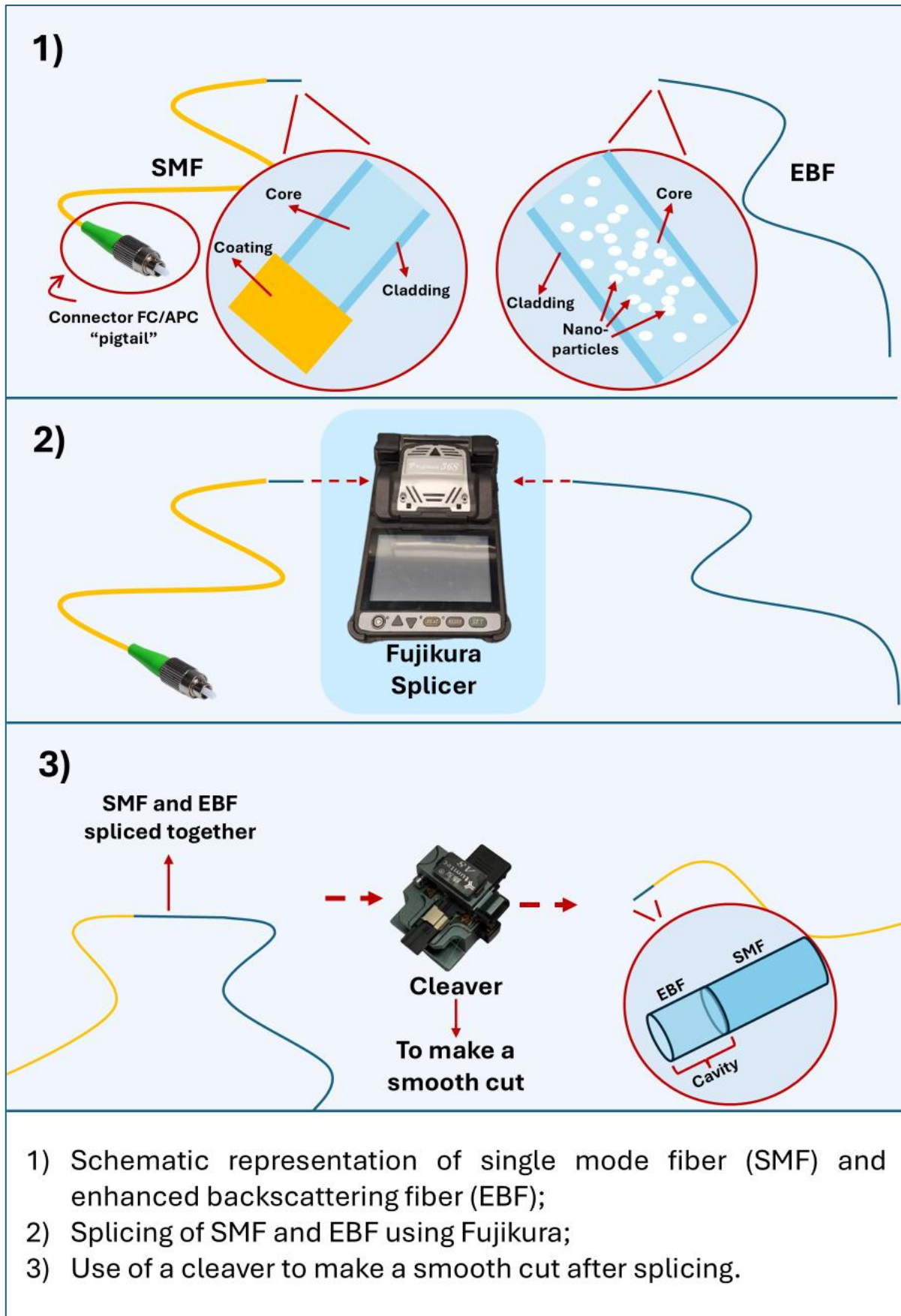


Figure 3.2: Schematic representation of sensor fabrication

3.2 Calibration of Optical Fiber Sensors

After the sensors are manufactured, they must be calibrated. To do this, the sensors must be connected to the channels of the Micron Optics interrogator. Micron Optics generates light using a laser. SDI sensors are connected to the channels of Micron Optics. Depending on the environment, the value of the refractive index varies for the SDI sensor, and the Micron Optics interrogator registers this [13,14].

After connecting using software ENLIGHT, sensors can be evaluated. A sensor that will have a high sensitivity, fabricated according to the method of this work, will have a certain wave. The waves should be higher or equal to -40 along the Power axis and should not be noisy. Figure 3.3 shows the wavelength of a sensor with high sensitivity.



Figure 3.3: Example of spectrum of the sensor with high sensitivity

After visual selection of the sensor, it is necessary to prepare the staff for calibration. For calibration, it's necessary to prepare sucrose 40%, sucrose 10%, pipettes, pipette tips, caps with sensor slots or tubes with a plastic stick. Figure 3.4 schematically shows the sensor calibration setup.

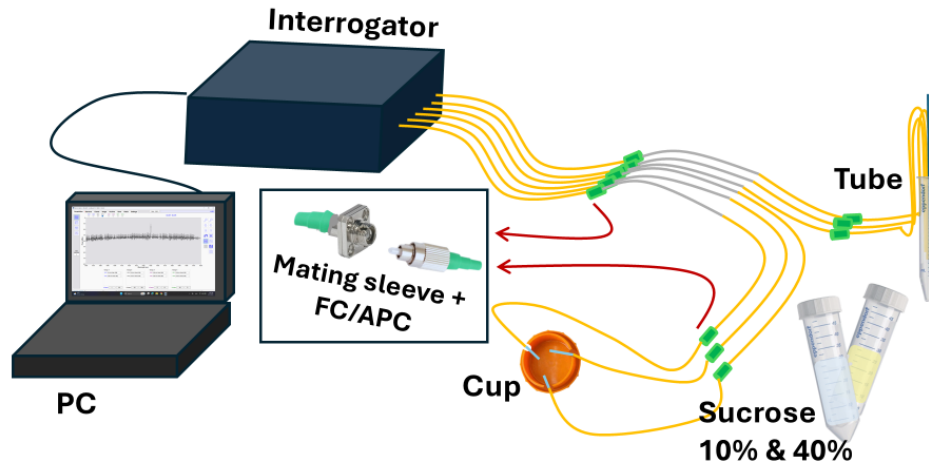


Figure 3.4: Schematic representation of calibration process

To evaluate the sensitivity of the sensor, a MATLAB script was used [1], which is commonly used in the Biosensor laboratory. It was necessary to make 6 measurements. With each measurement the sucrose concentration increased. The first measurement was 6 mL of 10% sucrose; 400 μ L of 40% sucrose were added from the second to the sixth measurement. Each measurement was saved in text format through the ENLIGHT program. Next, 6 measurements were uploaded to MATLAB to obtain sensitivity results. An example of one of the calibrated sensors is shown in Figure 3.5.

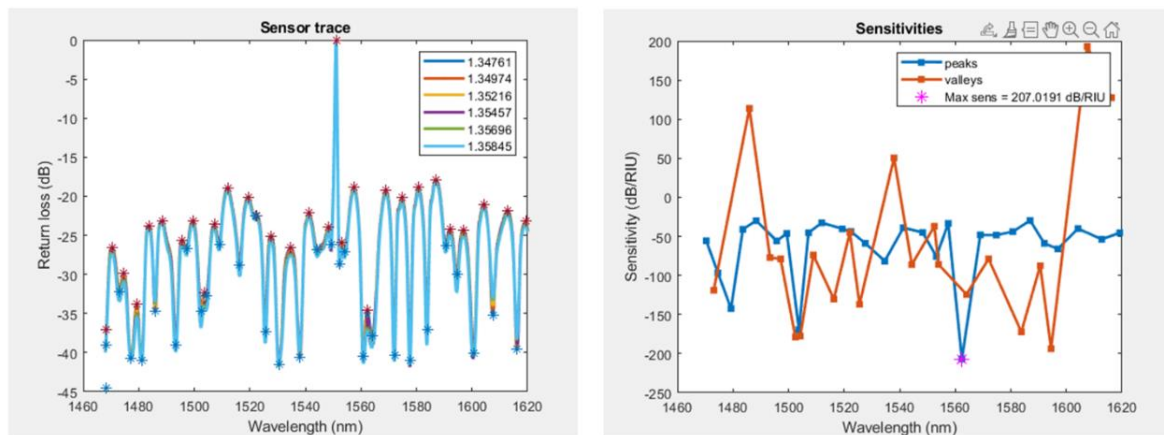


Figure 3.5: An example of the calibrated sensor

The wavelength of the sensor is shown on the left in Figure 3.5, the upper right corner is the concentration of sucrose, with increasing concentration, the intensity of each peak and valley changes [1, 12]. On the right, Figure 3.5 shows the best peaks and valleys of the calibrated sensor. After calibration, each sensor was sampled only with a sensitivity above 100 $d\beta/RIU$.

3.3 Functionalization of Optical Fiber Sensors

At the stage of functionalization, it is necessary to change the sensor surfaces so that it is specific to one target biomarker. In this study, experiments were conducted with variants of the biosensor surface functionalization, namely two variants of the sensor surface silanization with ((3-Aminopropyl)trimethoxysilane) APTMS [41] and m-PEG:amine [27], and the use of the semiconductor material perovskite with the formula $CsIFAIMACIMABrPbI_2$. Table 3.1 shows the stages of functionalization using APTMS at the silanization stage.

Table 3.1 The stages of functionalization with APTMS

Step	Reagents	Procedure
1	2	3
Cleaning the surface of the sensor	Sulfuric acid, hydrogen peroxide	Piranha solution was used in this work. Sulfuric acid and hydrogen peroxide were mixed in a glass tube in a ratio of 3 to 1. The sensors are mounted on a glass stick and placed in solution for 15-20 minutes.
Silanization	APTMS, methanol	After Piranha solution, the sensors must be rinsed with DI water and dried with N_2 stream. Next, it is necessary to put the sensors in a solution of APTMS in methanol. For a 5ml solution, it is necessary to take 50 μL of APTMS and 4.95 mL of Methanol. Leave the sensors in the solution for 30 minutes.

1	2	3
Heat-treatment	-	After silanization, the sensors must be rinsed in the solvent that was used (methanol). Next, the sensors were placed in the oven at 110°C for an hour.
Cross-linker	Glutaraldehyde (GA), buffer	After the oven, the sensors must be rinsed with clean water. Plastic Eppendorf tubes are used at the cross-linker stage. The work used GA because it contains aldehyde groups, these aldehyde groups react with amino groups of bioreceptors. In this works bioreceptors with amino groups were used. For solution it's necessary to take 500 μ L of GA and 500 μ L of phosphate-buffered saline buffer (PBS). Next, the sensors are placed in the solution and on a shaker for 1 hour at room temperature.
Bioreceptor immobilization	Stock with bioreceptors, buffer	After the cross linker, wash sensors with the buffer. Next -put sensors in a solution with bioreceptors. The solution contains aptamer or an antibody of the required concentration and a buffer. The sensors are placed in a solution and in a shaker at room temperature, for an hour if there is an antibody and for 4 hours if there is an aptamer.
M-blocking	m-PEG, buffer	After the immobilization stage, the sensor is washed with a buffer. In this work, m-peg was used for m-blocking.

Experiments where silanization took place using the APTMS method always lasted longer than the option with m-PEG:amine. Table 3.2 shows the stages of functionalization with m-PEG:amine silanization. For experiments with perovskite, the method of silanization with APTMS was used, but before the silanization stage, a layer of lead iodate, and then organic salt was applied to the sensor surface.

Table 3.2 The stages of functionalization with c m-PEG:amine

Step	Reagents	Procedure
Cleaning the surface of the sensor	Sulfuric acid, hydrogen peroxide	Piranha solution was used in this work. Sulfuric acid and hydrogen peroxide were mixed in a glass tube in a ratio of 3 to 1. The sensors are mounted on a glass stick and placed in solution for 15-20 minutes.
Silanization	m-PEG:amine, toluene	m-PEG:amine solutions are dissolved in toluene at the required concentration. Leave the sensors in the solution for 30 minutes.
Heat-treatment	-	After silanization, the sensors must be rinsed in the solvent that was used (toluene). Next, the sensors were placed in the oven at 110°C for 10 minutes.
Bioreceptor immobilization	Stock with bioreceptors, buffer	After the cross linker, wash sensors with the buffer. Next -put sensors in a solution with bioreceptors. The solution contains aptamer or an antibody of the required concentration and a buffer. The sensors are placed in a solution and in a shaker at room temperature, for an hour if there is an antibody and for 4 hours if there is an aptamer.

The process of preparing the two formulations for perovskite used in this work is shown in Table 3.3.

Table 3.3 Perovskite solution preparation

Solution	Reagents	Procedure
1	2	3
CsI/PbI ₂	PbI ₂ CsI DMF(N-Dimethylformamide) DMSO (Dimethylsulfoxide)	To PbI ₂ powder (600.6 mg) add 950 uL of DMF. To CsI powder (390mg) add 1mL DMSO. To prepare a solution add to 950µL of PbI ₂ in DMF 50µL of CsI solution in DMSO [42].

1	2	3
Organic salt	<i>FAI</i> <i>MACl</i> <i>MABr</i> <i>IPA</i>	Add FAI (60 mg), MACl (6 mg), MABr (6 mg) to the vial. Dissolve in 1 ml of IPA. The color of the liquid should be transparent [42].

When working with perovskite, it is necessary to keep the solution fresh, if the organic salt solution turns yellow, a new one must be prepared, and the solution with may CsI/PbI₂ begin to solidify. Figure 3.6 presents two liquids: organic salt and CsI/PbI₂ solution.

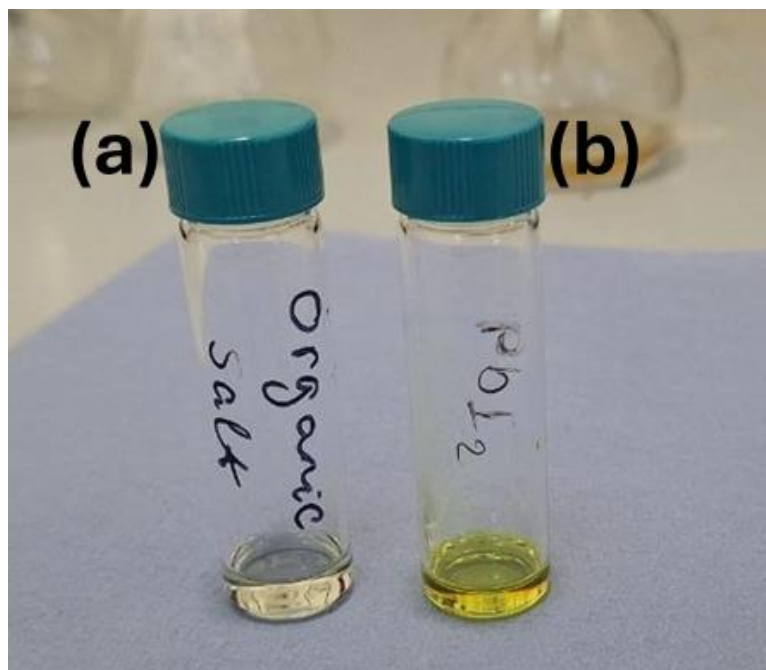


Figure 3.6: Solutions for perovskite coating: (a)organic salt mixture (*FAI/MACl/MABr*) and (b)*CsI/PbI₂*

If the deep coating procedure with the sensor is performed correctly, the tips of the sensor will darken due to the reaction of lead and organic salt. For the functionalization option using perovskite, the protocol shown in Table 3.4 was used.

Table 3.4 The stages of functionalization with c Perovskite

Step	Reagents	Procedure
1	2	3
Cleaning the surface of the sensor	Sulfuric acid, hydrogen peroxide	Piranha solution was used in this work. Sulfuric acid and hydrogen peroxide were mixed in a glass tube in a ratio of 3 to 1. The sensors are mounted on a glass stick and placed in solution for 15-20 minutes.
Applying perovskite to the sensor surface	Organic salt, CsI/ PbI ₂	After Piranha solution, sensors must be rinsed with DI water and dried with N ₂ stream. Each sensor is first dipped in a solution with CsI/PbI ₂ for 30 seconds, then in organic salt for 30 seconds. Next, the sensors are placed in the oven for half an hour at a temperature of 70 degrees.
Encapsulation with PMMA (poly(methyl methacrylate)) [43]	PMMA dissolved in Chloroform	It is necessary to encapsulate the sensor surface after perovskite using PMMA. 2 mg of PMMA was dissolved in 1 ml of Chloroform. To apply to the sensor, deep coating method was used, put each sensor into the solution for 2 seconds.
Silanization	APTMS, methanol	After Piranha solution, the sensors must be rinsed with DI water and dried with N ₂ stream. Next, it is necessary to put the sensors in a solution of APTMS in methanol. For a 5ml solution, it is necessary to take 50 µL of APTMS and 4.95 mL of Methanol. Leave the sensors in the solution for 30 minutes.
Heat-treatment	-	After silanization, the sensors must be rinsed in the solvent that was used (methanol). Next, the sensors were placed in the oven at 110°C for an hour.
Cross-linker	Glutaraldehyde (GA), buffer	After the oven, the sensors must be rinsed with clean water. Plastic Eppendorf tubes are used at the cross-linker stage. The work used GA because it contains aldehyde groups, these aldehyde groups react with amino groups of bioreceptors. In this works

1	2	3
		bioreceptors with amino groups were used. For solution it's necessary to take 500 μ L of GA and 500 μ L of phosphate-buffered saline buffer (PBS). Next, the sensors are placed in the solution and on a shaker for 1 hour at room temperature.
Bioreceptor immobilization	Stock with bioreceptors, buffer	After the cross linker, wash sensors with the buffer. Next -put sensors in a solution with bioreceptors. The solution contains aptamer or an antibody of the required concentration and a buffer. The sensors are placed in a solution and in a shaker at room temperature, for an hour if there is an antibody and for 4 hours if there is an aptamer.
M-blocking	m-PEG, buffer	After the immobilization stage, the sensor is washed with a buffer. In this work, m-peg was used for m-blocking.

After completing the functionalization stage, detection can be performed immediately, or sensors can be stored in a buffer for a couple of days and measurements can be performed.

3.4 Detection Procedure and Data Analysis

In this study, detection was carried out using a Micon Optics interrogator. For detection, Eppendorf 2 ml caps were used, in which a hole was made for the sensor. The sensors were connected to the interrogator channels. To create concentrations, the method Serial Dilution was used, when we gradually reduce the concentration through successive and serial transfusions. For each concentration, 30 measurements were made, each measurement lasted 45 seconds.

In this work, the MATLAB code [1], used for laboratory detection analysis, is modified. The goal is to automate it and make the user friendly. The principles are identical, but the Python

programming language was used. First, it is necessary to download all the stored concentration data. The interrogator recorded each concentration in the wavelength range of 1460-1620 nm, each measurement contains a wavelength value (nm) and an intensity value (dB). In order to estimate the spectrum, it is necessary to suppress noise. For this purpose, the Savitsky-Golay filter was used in this work [7-11]. As a result of the checks, the best option is a value of 51 for the window width, and a value of 3 for the order of the polynomial. Secondly, the user is prompted to interactively remove the FBG (Fiber Bragg Grating) peak so that it does not appear during further analysis (Figure 3.7).

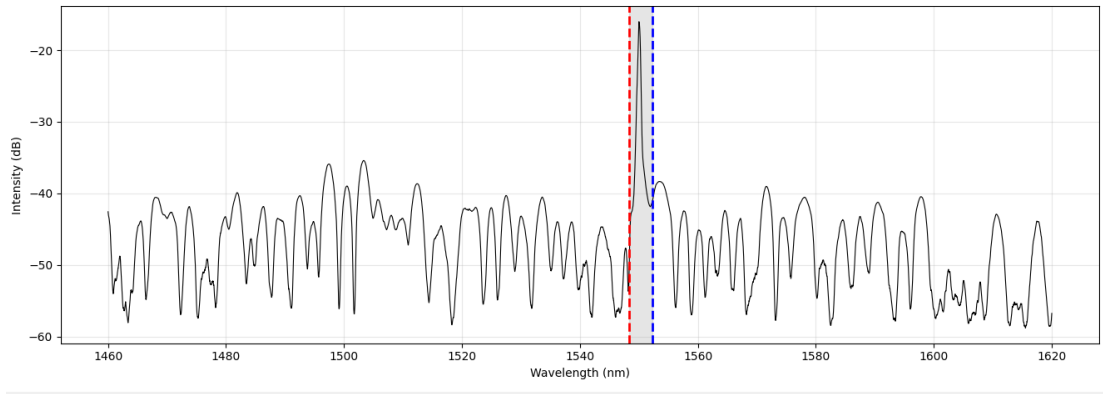


Figure 3.7: FBG peak removing

In order to remove FBG, the user needs to click on the borders of this peak on the left and right, then close the window. This method will facilitate the analysis process, because the user does not need to manually specify in the code the location of the FBG peak in wavelength. Next, the user can manually evaluate the spectrum after removing the FBG. The user can zoom in the peaks for evaluation. Using the Savitsky-Golay filter preserves the shape of peaks and valleys as much as possible [11]. Figure 3.8. shows manual spectrum analysis.

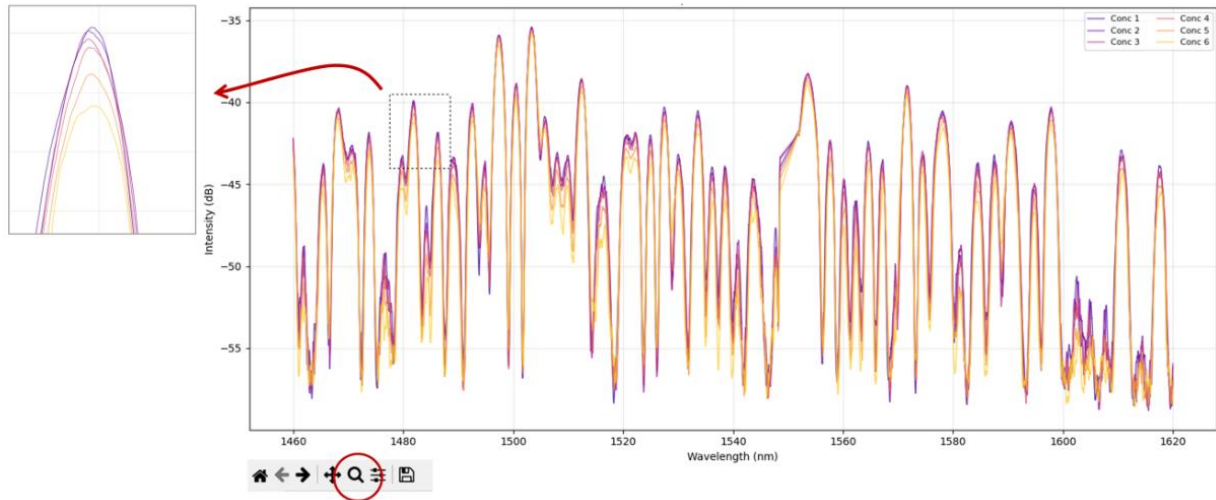


Figure 3.8: Spectrum analysis

The user is presented with graphs of concentration changes in intensity and time. Also, the average of the left and right peaks, the average of the left and right valleys. Figure 3.9 shows an example of the average of the left and right peaks, and identical graphs are obtained for the valleys.

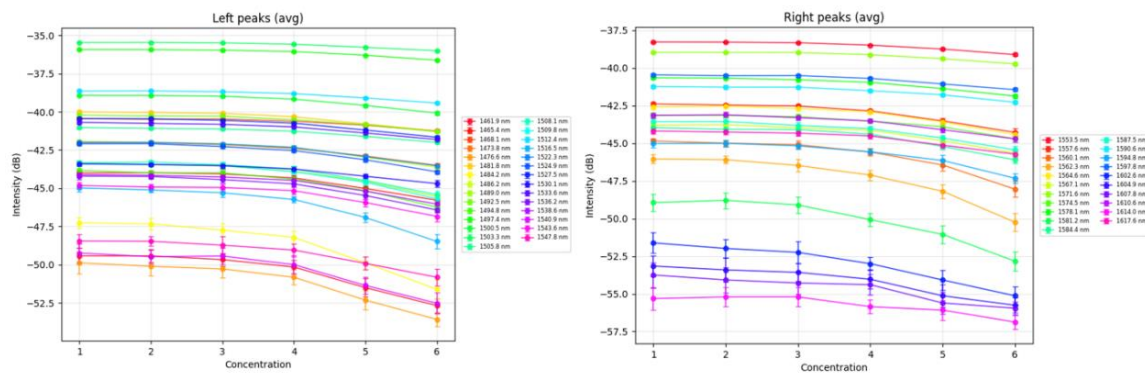


Figure 3.9: Spectrum analysis

Complete representation of each peak by points is presented in Appendix A – peaks, Appendix B – valleys. Where each point is one dimension. And there are usually 30

measurements in one concentration. The LOD search is carried out according to the logic of the MATLAB code [1], but there is a possibility of manual and automatic search.

Chapter 4

Results and Discussion

4.1 Alpha-synuclein results

In this work, experiments were conducted with alpha-synuclein. The peptides Alpha-synuclein (phospho S129) peptide and Recombinant Anti-alpha-synuclein (phosphoS129) antibody were used for the work. Alpha-synuclein (phospho S129) peptide mimics a protein region and was targeted by an analyte. Recombinant Anti-alpha-synuclein (phosphoS129) antibody is an antibody that specifically binds to phospho S129.

In the first experiment, various functionalization methods were evaluated. Namely, functionalization with silanization of APTMS, silane-PEG, m-PEG:amine with 2:1 and 4:1 ratio. Table 4.1 shows the data on the sensors that were fabricated for the first experiment, the sensitivity of the sensors, and which method was used on the sensor.

Table 4.1 Sensors and functionalization method

Sensor №	Sensitivity	Method
1 (13)	138.76	Silane-PEG
2 (18)	215.50	m-PEG:amine (4:1)
3 (19)	182.80	m-PEG:amine (2:1)
4 (20)	249.90	APTMS 1%

In the first column, the actual sensor numbers are shown in parentheses, but for the convenience of describing the work, numbers 1, 2, 3, and 4 will be used. Table 4.2 shows the concentration with which the experiment was conducted.

Table 4.2 Concentrations for the first experiment

№	Concentrations
1	2
1	Buffer (PBS)
2	0.0156 pg/ml
3	0.156 pg/ml
4	1.56 pg/ml
5	15.63 pg/ml
6	156.25 pg/ml
7	1562 pg/ml
8	15625 pg/ml
9	156250 pg/ml
10	1562500 pg/ml
11	15625000 pg/ml

For the Silane-PEG, m-PEG:amine (4:1), and m-PEG:amine (2:1) experiments, toluene was used to dissolve the powders. To do this, sieve molecules were added to toluene in advance to remove all the water. The sensor functionalized by the Silane-PEG method showed a good response based on graphs of changes in the intensity value with changes in concentrations. For the Silane-PEG method, the maximum change across all concentrations was 0.007 RIU (1dβ). Figures 4.1 and 4.2 show the average value for changes in peaks and valleys.

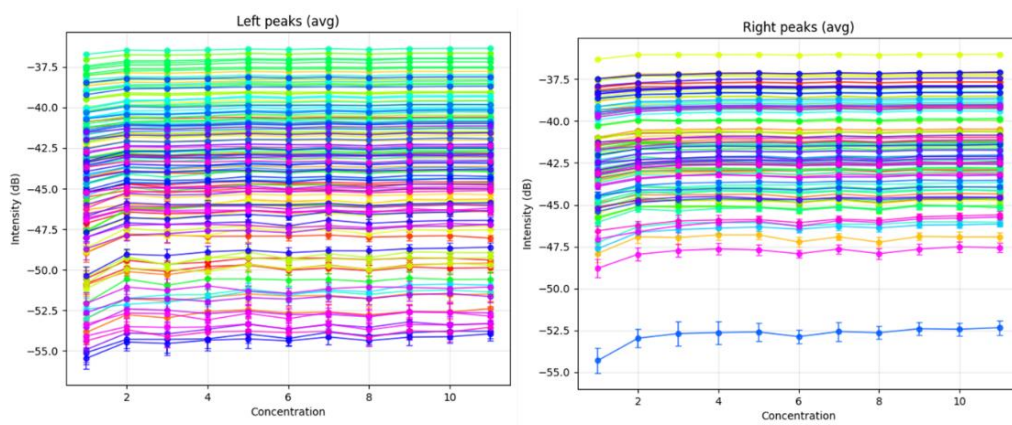


Figure 4.1 Sensor №1 peaks (Silane-PEG method)

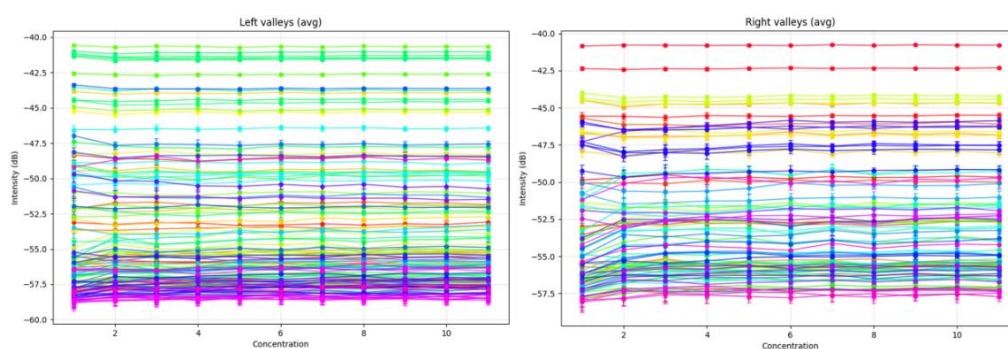


Figure 4.2 Sensor №1 valleys (Silane-PEG method)

Figure 4.3 shows the weighted linear fit (left) and weighted linear fit (right) charts. The LOD value for Silane-PEG method is 93 pg/ml.

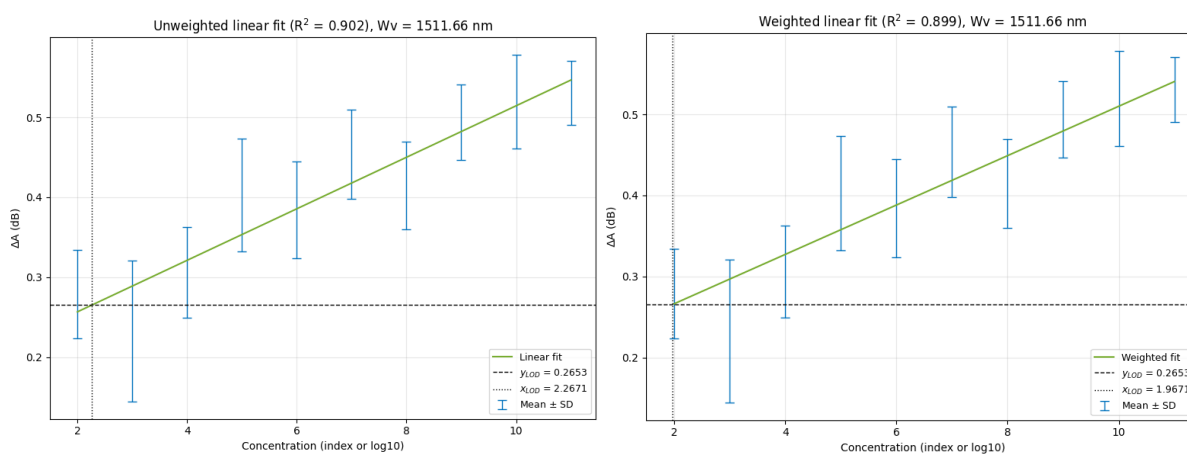


Figure 4.3 Sensor №1 LOD graphs (Silane-PEG method)

For the m-PEG:amine (4:1) method, the maximum change across all concentrations was less than 0.004 RIU (less than 1d β of changes). For the APTMS method, the sensor showed changes of 0.004 RIU (1 d β). The sensor functionalized by the m-PEG:amine (2:1) method showed the best option among all the methods. Figure 4.4 shows the change in peaks for all concentrations. Next, the LOD value was determined based on the peaks.

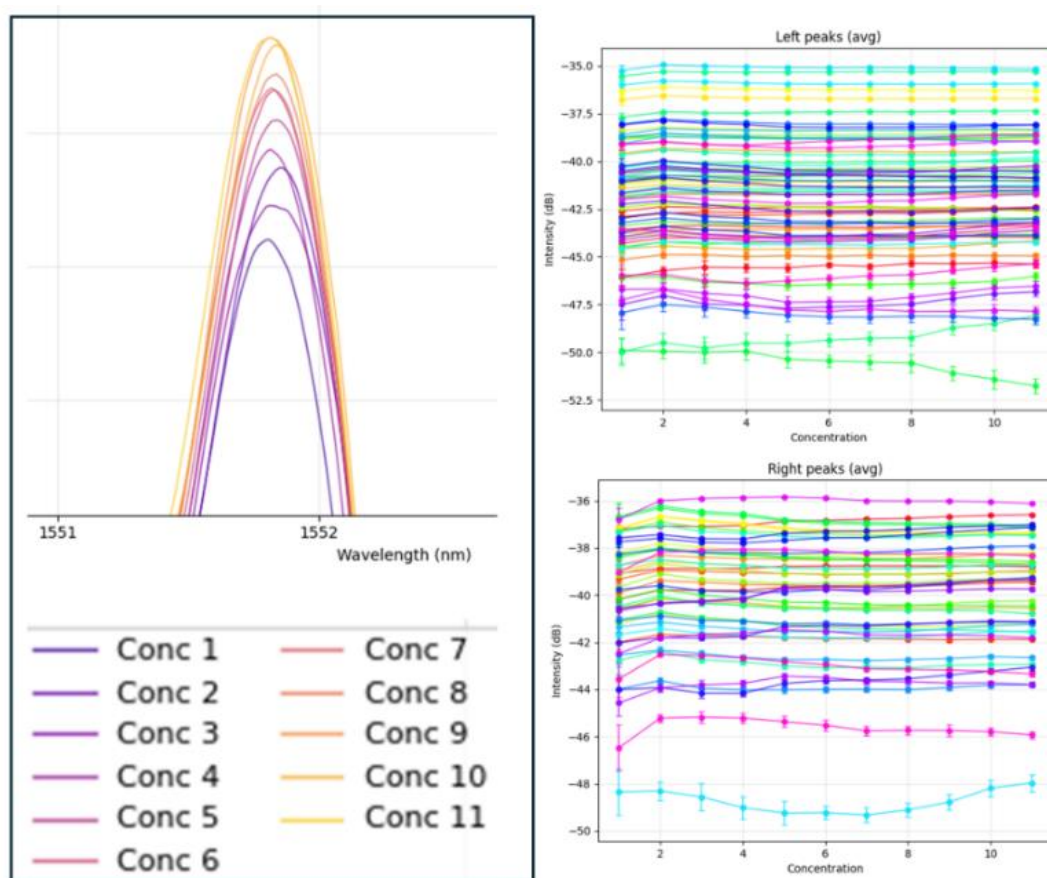


Figure 4.4 Sensor №3 peaks (m-PEG:amine (2:1))

The best method of functionalization turned out to be m-PEG:amine (2:1). This method not only saved the experiment time but also enhanced the sensor signal. The LOD value for the m-PEG:amine (2:1) method was determined from the peaks of Sensor №3. The LOD value for the unweighted fit was 415.64 pg/ml, and for the weighted fit it was 352.32 pg/ml. Based on the LOD graphs, it can be concluded that the detection using the m-PEG:amine (2:1) method

showed a better result than the Silane-PEG method, the sensor measurements of the functionalized m-PEG:amine (2:1) have more stable measurements, the standard deviation is small. Figures 4.5 and 4.6 show the current chart, Figure 4.5 weighted fit, Figure 4.6 weighted fit.

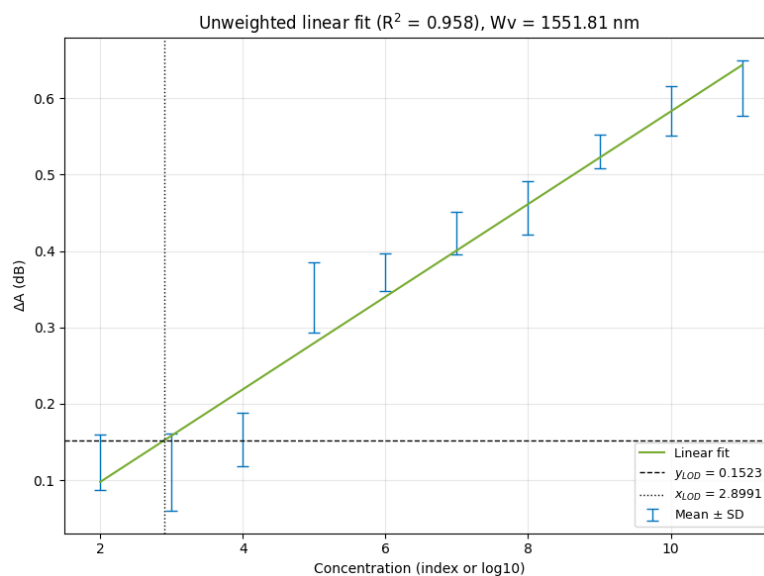


Figure 4.5 Sensor №3 Unweighted linear fit

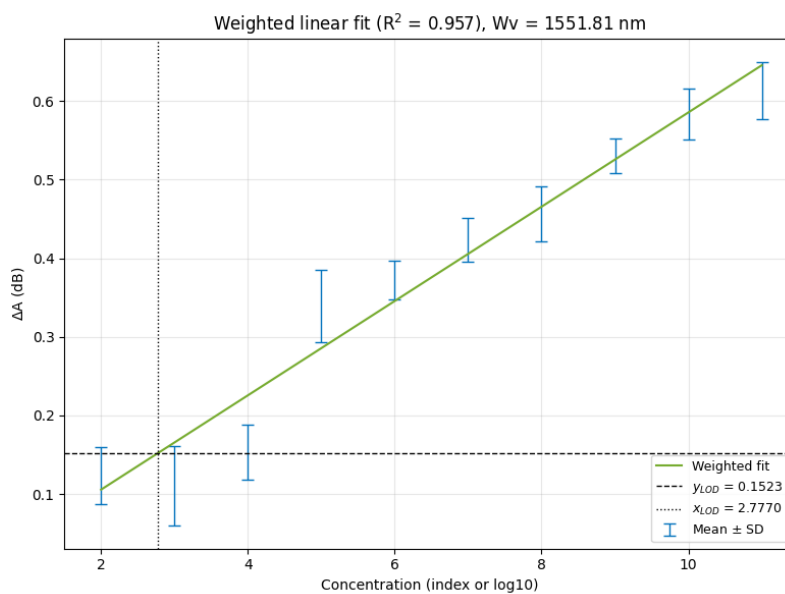


Figure 4.6 Sensor №3 Weighted linear fit

Since the m-PEG:amine (2:1) method showed the best results, an experiment with negative control was conducted. The sensors were functionalized using an identical method, with the exception of the antibody immobilization step. Antibodies were not applied to some sensors to check whether the response of sensor №3 was due to binding at the biomolecular level or there were other reasons. As a result, it was found that the sensors without antibodies showed no change in concentrations, therefore, the response shown by sensor №3 was solely due to the binding of the antibody to the protein. An example of a sensor without antibodies is shown in Figure 4.7. As you can see on the graphs, there are no changes in concentration at either peaks or valleys.

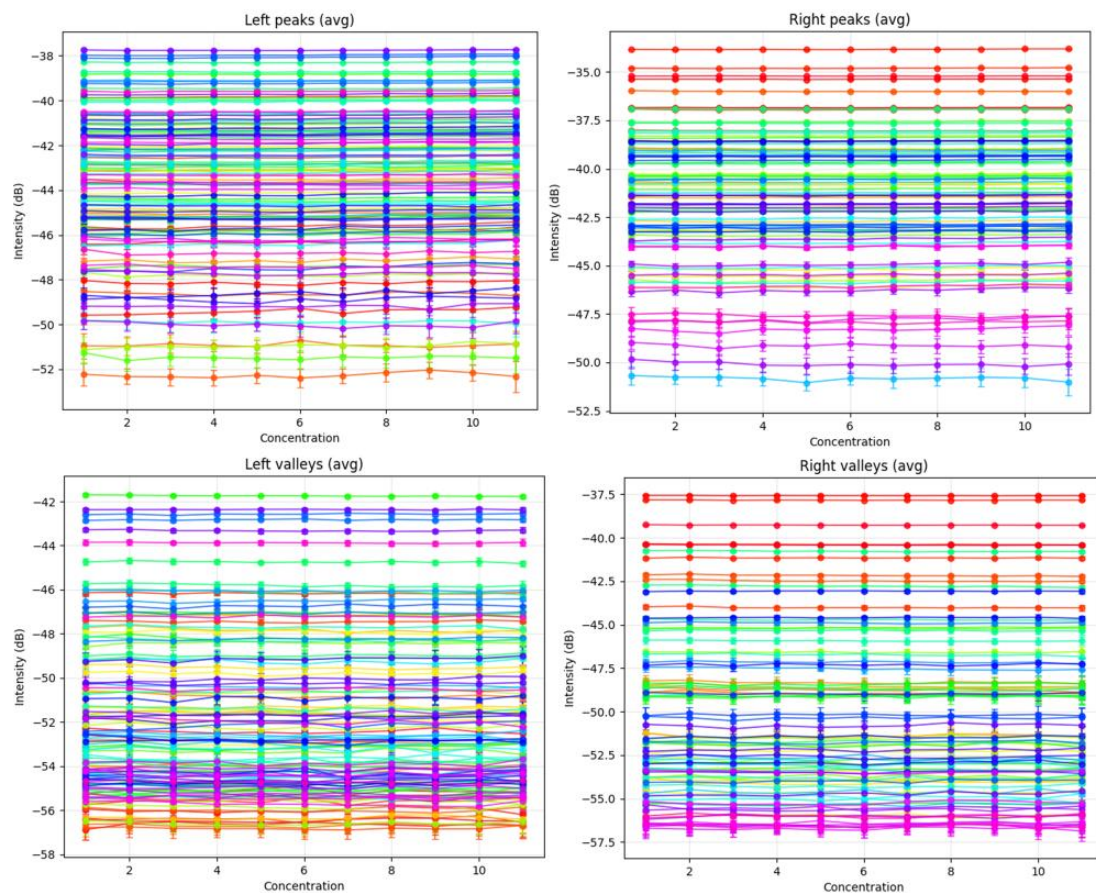


Figure 4.7 Sensor functionalized by m-PEG:amine (2:1) without antibody immobilization

The graphs of Figure 4.7 show that the intensity value does not change with increasing concentration, therefore, the sensor showed a good result with negative control, which means results obtained in previous experiments were due to biomolecular interaction.

Due to the absence of pure toluene, experiments with m-PEG:amine (2:1) were temporarily stopped, as the powders did not dissolve. Instead, a variant of the APTMS experiment was tested, but with signal amplification due to the semiconductor material perovskite. In the first experiment with perovskite, there were experiments using PMMA and without PMMA. The results are presented in Table 4.3.

Table 4.3 Perovskite functionanlization results

Sensor №	Procedure	Results
1	2	3
1 (25)	With PMMA encapsulation	Sensors with PMMA encapsulation showed higher response. Sensor №3 average response peaks presents in Figure 4.8.
2 (19)		
3 (20)		
4 (7)		
5 (17)	Without PMMA encapsulation	Sensors without PMMA encapsulation showed lower response. Sensor №5 average response peaks presents in Figure 4.9.
6 (5)		
7 (14)		
8 (38)		

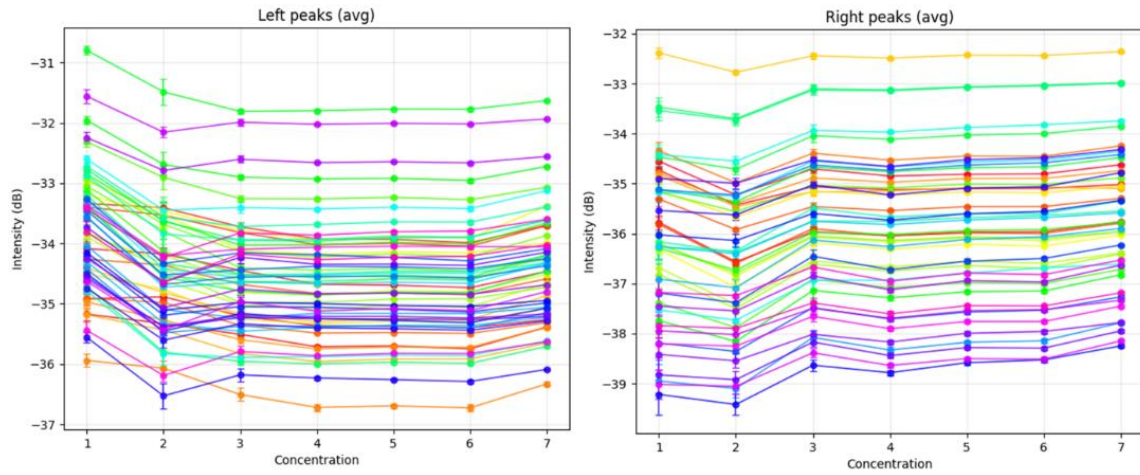


Figure 4.8: Sensor №3 encapsulated with PMMA average response peaks

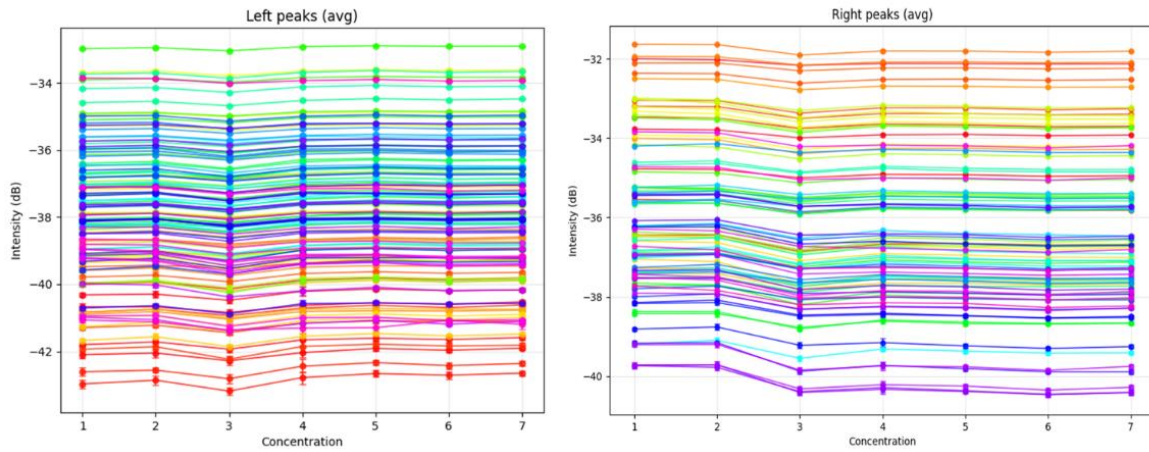


Figure 4.9: Sensor №5 (no PMMA) average response peaks

As can be seen in the graphs (Figures 4.8, 4.9), the sensor with PMMA encapsulation gave a greater response, while the perovskite from the sensor without encapsulation presumably degraded, since perovskite is a hydrophobic material, and the component of any buffer is water. Later, a method with encapsulation of a perovskite layer with PMMA was used for experiments. Table 4.4 shows the concentrations for the perovskite experiment, where all sensors were encapsulated with PMMA.

Table 4.4 Concentrations for the perovskite experiment

№	Concentrations
1	2
1	Buffer (PBS)
2	31.25 pg/ml
3	312.5 pg/ml
4	3.125 ng/ml
5	31.25 ng/ml
6	312.5 ng/ml
7	3.125 ug/ml

As a result of the experiment, the LOD value for the uweighted fit was 2.09 ng/ml (Figure 4.10), for the weighted fit 3.01 ng/ml (Figure 4.11). The values obtained are not a clinical standard for a biosensor.

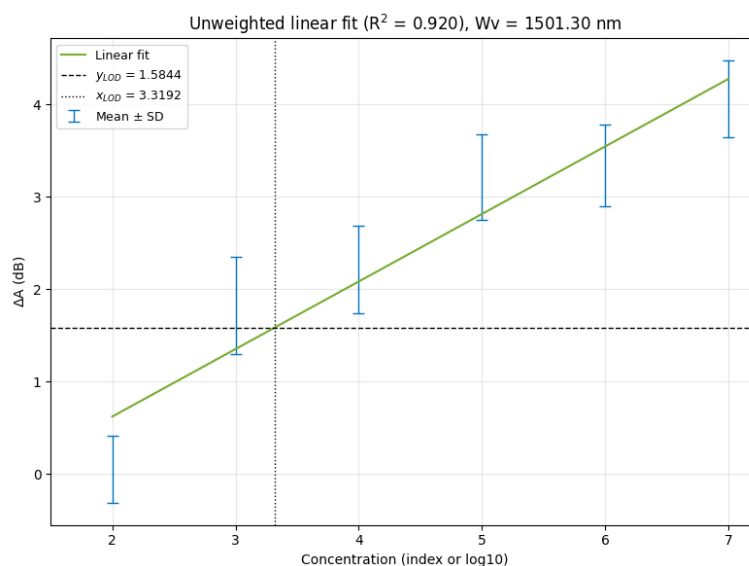


Figure 4.10: Unweighted linear fit for perovskite functionalization with PMMA encapsulation

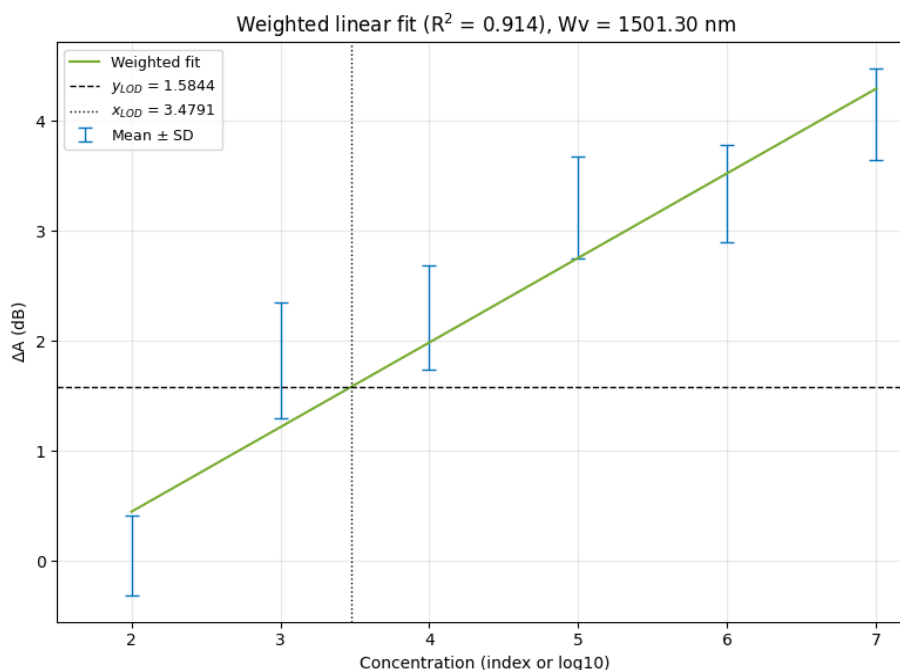


Figure 4.11: Weighted linear fit for perovskite functionalization with PMMA encapsulation

Experiments with perovskite have shown better results than APTMS, but stability estimates are worse than m-PEG:amine (2:1). The results of m-PEG:amine (2:1) showed high responsiveness and stability. In further experiments with perovskite, it is necessary to check the functionalization with perovskite for negative control. Also, to resume experiments with the functionalization of m-PEG:amine (2:1).

4.2 Progesterone results

For experiments with progesterone, the GQ-5 aptamer was used as a bioreceptor. The aptamer was purchased in a powder form. To obtain a concentration of 100 μM , 280 μL of sterile water was added, then the stock was poured into aliquots of 12 μL . The entire procedure took place in a sterile box; all instruments were pre-cleaned with 70% ethanol. Concentrations of 1 μM and 3 μM were used to immobilize the aptamers on the sensor. A KCl buffer was used

to dilute the desired concentration, since the GQ-5 aptamer has a G-quadruplex structure, K^+ [44] is required. Table 4.5 shows the buffer preparation method and the concentration of aptamers for immobilization on the sensor surface.

Table 4.5 Solutions preparation

Solution	Preparation	Comments
1	2	3
KCl buffer (200mL)	Tris-HCl (1M): 2 mL KCl (powder): 744 mg Add DI water up to 200 mL	For G-quadruplex is better to use K^+ [44, 37]. Value of pH of the buffer should be 7-7.4 pH
1uM GQ-5	GQ-5 aliquot (100uM): 5 μ L KCl buffer: 495 μ L	1uM concentration was used since in the article Bekmurzayeva et al. [41] was used 0.5 μ M concentration of aptamers for their target – thrombin
3uM GQ-5	GQ-5 aliquot (100uM): 15 μ L KCl buffer: 485 μ L	3 μ M concentration was used for experiments because in the article Kumar et al. [37] for their experiments with GQ-5 aptamer used 3 μ M concentration

Progesterone in Prolutex solution was used as a target analyte. Prolutex contains progesterone at a concentration of 70 mg, also contains hydroxypropylbetadex and water for injections. In the experiments, APTMS was used for functionalization. The aptamer immobilization lasted 4 hours in a shaker, the solution of aptamers in buffer was annealed at 95 degrees for 7 minutes and then cooled to room temperature. For the first experiment, the concentration of the aptamer GQ-5 1uM was used. Concentrations of progesterone were used in clinical ranges and are shown in the table

Table 4.6. Clinical progesterone concentrations for the experiment

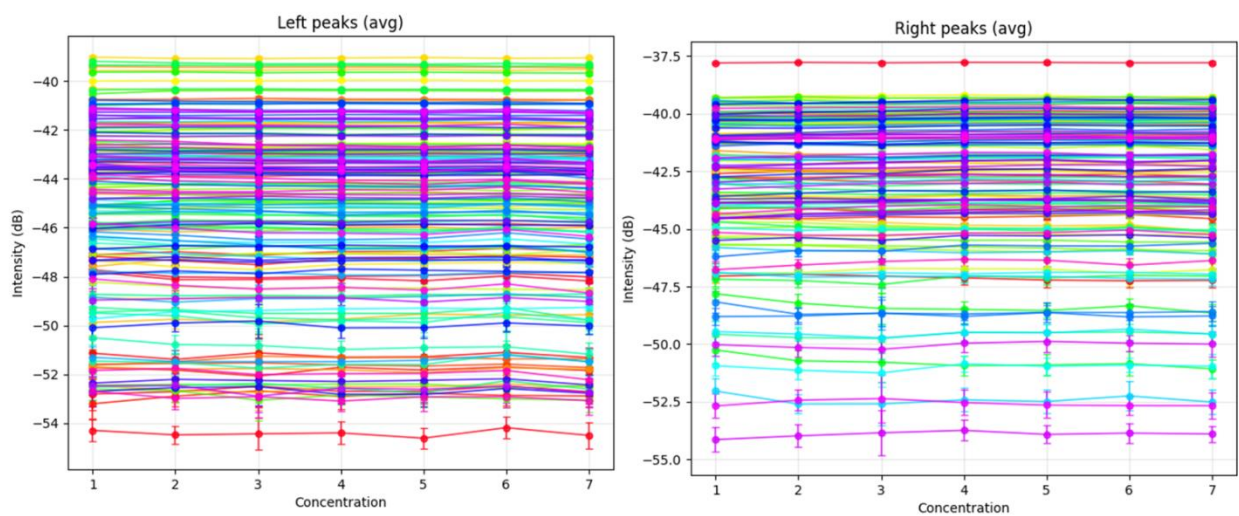
№	Concentrations
1	2
1	Buffer (PBS)
2	0.01 nM
3	0.1 nM
4	1 nM
5	10 nM
6	100 nM
7	1 uM

For detection in each concentration, 30 measurements were carried out, the duration of one measurement was 45 seconds. As a result, the maximum change across all concentrations was 0.0008 RIU, which is not a good indicator for the experiment. The experimental results are presented in Table 4.7.

Table 4.7 Experiment results with aptamer GQ-5 concentration 1 μ M

Sensor №	Sensitivity d β /RIU	Aptamer concentration	Sensor response across all concentrations (RIU)
1	2	3	4
1 (18)	121.4952	1 μ M	0.0006
2 (17)	120.7062	1 μ M	0.0006
3 (20)	112.9831	1 μ M	0.0007
4 (22)	113.592	1 μ M	0.0008
5 (40)	159.1568	1 μ M	0.0001
6 (31)	118.664	1 μ M	0.0006
7 (27)	115.7243	1 μ M	0.0006

The graphs of peaks and valleys show that the intensity of the sensor through concentration is stable. Figure 4.12 shows the average peak response of sensor №1. The other sensors have similar graphs and results.

**Figure 4.12: Sensor №1 average response (peaks)**

There were small changes, but they were insignificant. It can be assumed that the concentration of aptamers immobilized on the sensor surface was insufficient, or the concentration of progesterone was insufficient for detection by the biosensor. For the next experiment, the same concentrations were used as shown in Table 4.6. GQ-5 aptamer concentrations of 1 μ M and 3 μ M were used. The number of measurements and the time for each measurement were used for detection, identical to the first experiment. The purpose of the experiment was to compare whether there is a difference between the concentrations of aptamers for immobilization on the sensor. Table 4.8 shows the sensitivity of the sensors used, the concentration of polymers used, and the result.

Table 4.8 Experiment results with different concentrations of aptamer GQ-5

Sensor №	Sensitivity d β /RIU	Aptamer concentration	Sensor response across all concentrations (RIU)
1	2	3	4
1 (22)	105.7767	1 μ M	0.0009
2 (40)	118.8045	1 μ M	0.0009
3 (7)	138.3971	1 μ M	0.0003
4 (12)	115.3101	1 μ M	0.0009
5 (19)	101.2839	3 μ M	0.002
6 (13)	145.0442	3 μ M	0.0009
7 (25)	165.7238	3 μ M	0.001
8 (31)	126.2355	3 μ M	0.0004

Since the experiment with different concentrations did not produce strong changes, it was decided to test the possibility of binding the aptamer to progesterone from Prolutex. The maximum concentrations of Prolutex used for this experiment are shown in Table 4.9.

Table 4.9. High progesterone concentrations for the experiment

№	Concentrations
1	KCl Buffer
2	4.375 μM
3	8.75 μM
4	17.5 μM
5	35 μM
6	70 μM

For the experiment, an aptamer with a concentration of 1 μM was immobilized on the surface of the sensors. As a result, the sensors showed a high response through concentration. Table 4.10 shows the data on the result of the experiment.

Table 4.10. Results of detection of high concentrations of progesterone

Sensor №	Sensitivity $d\beta/\text{RIU}$	Aptamer concentration	Result
1	2	3	4
1 (18)	123.92	1 μM	0.01
2 (9)	121.2373	1 μM	0.01
3 (20)	135. 4339	1 μM	0.01
4 (4)	184.9019	1 μM	0.005
5 (40)	150.1703	1 μM	0.006

1	2	3	4
6 (25)	155.6996	1 μ M	0.006

The analysis of peaks and valleys showed changes in the intensity value through concentration, which was identical for all sensors. Figure 4.13 represents the average value of the peak intensity changes of sensor №1.

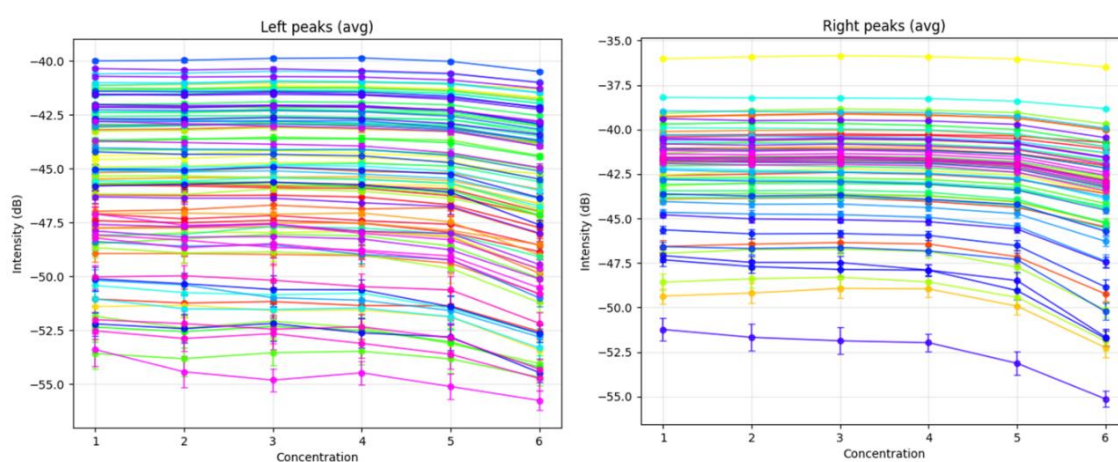


Figure 4.13: Sensor №1 average response to high concentration of progesterone (peaks)

To verify the results, it was decided to conduct an experiment without using aptamers, but to maintain high concentration. As a result, all sensors showed identical results to those with immobilized aptamers on the surface, therefore, the high response of the previous experiment is not related to biomolecular binding.

Chapter 5

Conclusion and Future Work

5.1 Summary of Main Findings

Optical fiber sensors with a sensitivity above 100 dB/RIU have been developed. The Micron Optics interrogator was used to analyze and register changes in refraction. As a result of the work, a promising method for functionalizing the surface of an optical fiber biosensor using m-PEG:amine was identified. With this method of functionalization, the LOD value for alpha synuclein was 415.64 pg/ml. This value is not a clinical standard, but it has prospects for development. Research on the use of optical fiber biosensor for progesterone detection is still at an early stage. The use of Progesterone in the Prolutex solution has created additional challenges for the sensor that need to be addressed. Experiments have been conducted with different types of bioreceptors. The antibodies showed stable results even if detection was performed a few days after functionalization. Aptamers, in turn, although they are less stable (in this work, when using aptamers, detection was carried out immediately after functionalization), are a cheaper analogue, which also show promising results.

5.2 Limitation of proposed sensor

Optical fiber biosensors are just an evolving method of obtaining analysis. Currently, there are limitations in the form of insufficient control, non-specificity, or response to other environmental parameters. Also, the optical structure of the fiber sensor is fragile and may break during analysis if additional interventions are not taken.

Progesterone detection studies are still at an early stage, the sensor with the current functionalization method lacks sensitivity at low analyte concentrations, and at high concentrations, even without aptamer immobilization, changes in intensity response values were observed. It is worth noting that although the fabrication of the optical fiber sensor itself takes about a minute, the functionalization time when using aptamers takes from 10 hours.

5.3 Future work

For the alpha-synuclein project, it is necessary to continue experiments with m-PEG:amine (2:1) as soon as the necessary reagents are available in the laboratory. It is also worth continuing experiments with signal amplification using semiconductors. In the future, there is a prospect of using the sensor for detection in the cerebrospinal fluid. For a progesterone project, first of all, check the value of the Prolutex refractive index on a refractrometer. Perhaps the results obtained in the last experiment are related to the high refractive index of Prolutex itself, since there are other injectable ingredients besides progesterone. For all projects, it is necessary to develop packaging in which the risk of sensor damage will be minimal and contact with biological fluids will be maximum.

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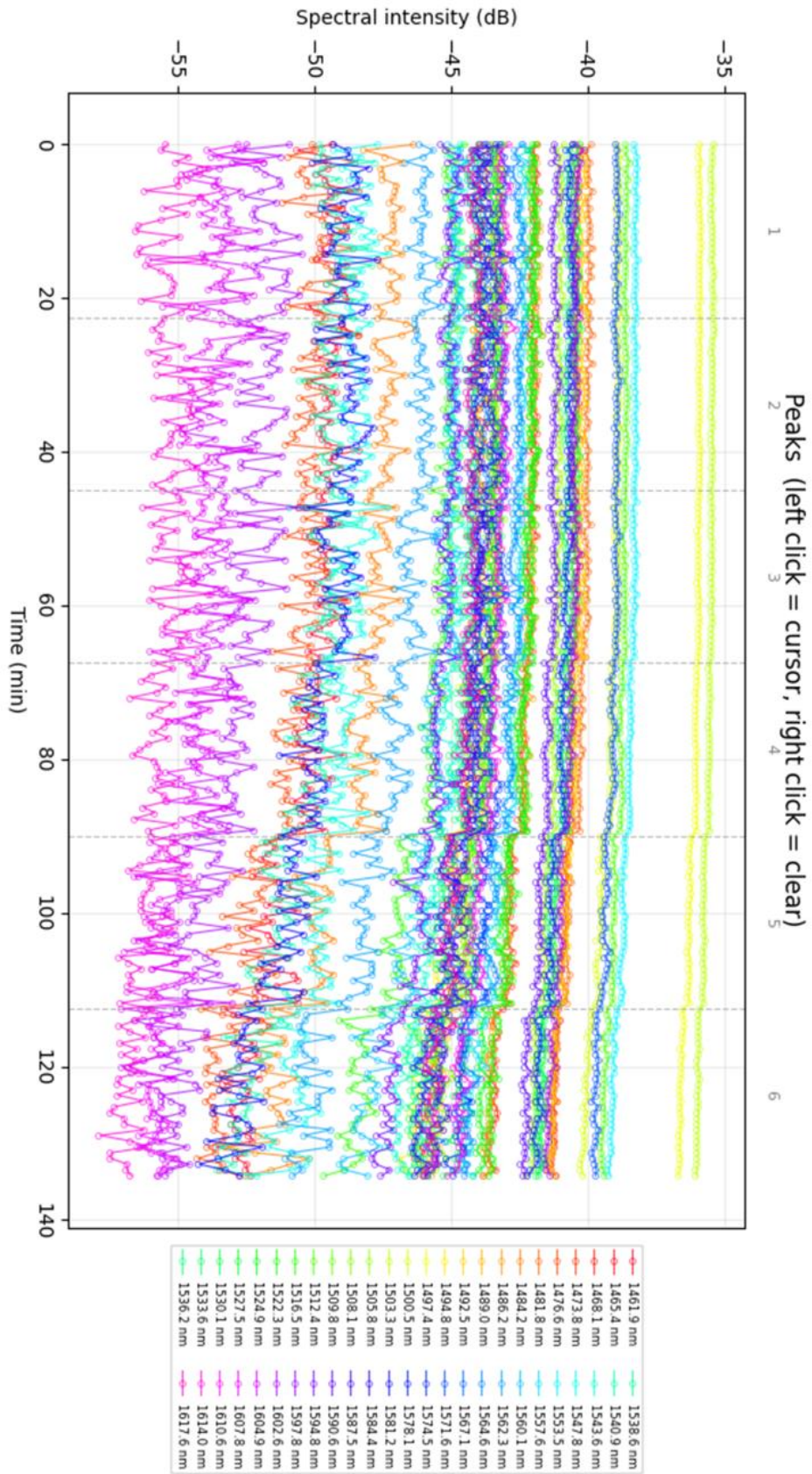
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Appendix A



Appendix B

