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Science in Electrical and Computer Engineering**



Nargiz Azat

**School of Engineering and Digital Sciences Department of Electrical and Computer
Engineering Nazarbayev University**

Application of Optical Fiber Sensors for IVF

Supervisor Name: Daniele Tosi

Co-supervisor Name: Carlo Molardi

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DECLARATION FORM

DECLARATION

I hereby, declare that this manuscript, entitled “Application of Optical Fiber Sensors for IVF”, 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.



Name: Nargiz Azat

Date: 30.03.2026

ABSTRACT

This paper presents the development, production, functionalization, and optimization based on signal processing of fiber-optic biosensors with semi-distributed interferometry (SDI) for the detection of interleukin-6 (IL-6), an inflammatory cytokine associated with endometriosis, without labels. The SDI design is based on partial Fresnel reflections at the junction between an enhanced backscattering (EBF) fiber and a standard single-mode fiber (SMF-28, 1550 nm), which creates a Fabry-Perot resonator with a sensitive length of about 500 microns. The interference of reflected optical signals creates a spectral band in which the wavelength shift correlates with changes in the refractive index of the environment (RI). Using sucrose solutions with six different refractive index levels (1.3476–1.3584 RIU), the sensor was calibrated using repeated measurements. Fourteen of the thirty-three sensors manufactured met the 60 nm/RIU sensitivity criteria. The selected sensors showed high sensitivity values of -116.95 nm/RIU ($R^2 = 0.90$) and 133.42 nm/RIU ($R^2 = 0.67$), indicating a compromise between linearity and sensitivity. When it came to tracking signals, it turned out that spectral troughs are more reliable than peaks.

To selectively detect IL-6, the surface was functionalized using a number of chemical treatments, including piranha purification, APTMS silanization, glutaraldehyde crosslinking, antibody immobilization, and mPEG blocking. To assess the stability and reproducibility of the signal, detection tests were performed at six concentration levels and data was re-collected.

To improve the signal quality, five signal processing methods were evaluated: Savicki–Golay baseline correction, wavelet-based noise reduction, Butterworth low-pass filtering, and Kalman filtering (standard and advanced). Detection limit (LoD), RMS error (RMSE), repeatability, sensitivity, signal-to-noise ratio (SNR), and Allan deviation were some of the metrics used to evaluate performance.

Compared to traditional methods, Kalman filtering showed the highest overall performance, providing a minimum LoD value of 26 micrograms/ml and significantly increasing signal stability. While traditional filtering methods either reduced sensitivity or distorted the signal, extended Kalman filtering produced equivalent results. In particular, the Sawicki–Golay correction led to non-physical behavior of the signal, despite its high apparent linearity, while Butterworth filtering led to excessive smoothness.

White noise prevails at short averaging intervals, but low-frequency drift becomes dominant over longer time intervals and, according to noise analysis using the Allan deviation, is inefficiently controlled by conventional filtering methods. In addition, signal-to-noise ratio analysis revealed nonlinear sensor behavior at intermediate concentrations, indicating limitations related to the dynamics of biomolecular interaction.

In general, the results show that recursive estimation based on the Kalman method is a very successful method for improving the efficiency of interferometric fiber-optic biosensors when operating in conditions of low signal-to-noise ratio. For reliable identification of low-concentration biomarkers in biomedical applications, modern signal processing must be integrated into the sensor design.

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DEFINITIONS

APTMS	(3-Aminopropyl)trimethoxysilane
ELISA	Enzyme-Linked Immunosorbent Assay
FPI	Fabry-Perot Interferometer
GA	Glutaraldehyde
IL-6	Interleukin-6
IL-8	Interleukin-8
LoD	Limit of Detection
mPEG	Methoxy-Polyethylene Glycol
MZI	Mach-Zehnder Interferometer
PBS	Phosphate-Buffered Saline
RI	Refractive Index
SDI	Semi-Distributed Interferometer
SMF	Single-Mode Fiber
SPR	Surface Plasmon Resonance

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1. INTRODUCTION

Endometriosis is a chronic autoimmune condition characterised by acute pelvic pain, infertility, and even depression, along with related health problems. Despite this effect and the disease's prevalence, its causes remain poorly understood. There is insufficient research on the treatment and diagnosis of non-invasive methods, leading to a demand for less invasive methods to detect the disease.

One alternative diagnostic approach is to study biomarkers of endometriosis. There are several theories of endometriosis pathophysiology, including the role of inflammatory cytokines. In particular, increased levels of IL-6 is observed in women with diagnosed endometriosis. Therefore, they can serve as potential biomarkers of endometriosis for early diagnosis, with high sensitivity at low concentrations. The accurate and rapid detection of these cytokines could provide valuable diagnostic information.

One of the traditional laboratory methods for analysis is ELISA, which, despite its high sensitivity, requires significant time and infrastructure. Thus, alternative methods are required that would give the same results at a lower cost.

Thus, optical biosensors have a huge advantage due to their portable diagnostic capabilities. Fiber-optic sensors, in particular, are compact and cheaper to manufacture and scale. Among them, fiber-optic interferometric sensors exhibit high sensitivity at low concentrations. One type of interferometer is the semi-distributed interferometer (SDI), which has an easy fabrication method despite its high sensitivity. This sensor is based on a similar interferometric structure to the Fabry-Perot interferometer. Interference between partially reflected optical signals enables the detection of the slightest changes in the environment. Having such high sensitivity to changes and resistance to electromagnetic influence, Semi-distributed Interferometer (SDI) sensors are a promising tool for biosensing.

Although fiber-optic biosensors offer many advantages, their use for detecting biomarkers, especially at low concentrations, remains under research. Most of the research concentrates on different concentrations and design optimisation. However, the effects of noise on sensors are not well understood, and there is a gap in signal processing research.

The novelty of the work is based on the use of signal processing in a semi-distributed interferometer to identify biomarkers at low concentrations. The aim is to develop optical sensors for detecting IL-6, with a focus on the signal-processing method.

2. LITERATURE REVIEW

2. 1. Biomarkers of Endometriosis

Endometriosis is a chronic disease associated with estrogen and the presence of endometrial tissue in other organs outside the uterus. Endometriosis occurs in 6 to 10 per cent of the female population of reproductive age [1][2]. The presence of the disease leads to a marked deterioration in the quality of life, along with the fact that about a third of all women additionally have infertility and 71-87% suffer from chronic pelvic pain [3]. Currently, laparoscopic examination and subsequent histological confirmation of the affected areas are the only confirmed options for diagnosing the disease. However, once endometriosis manifests, its diagnosis takes 10 years, indicating the lack of early diagnostic methods [4].

The lack of accurate data on endometriosis prevalence adds to the complexity. It is mainly associated with autoimmune causes, hormone imbalance, and inflammatory mechanisms [5]. This creates a process of lesion appearance and growth due to a weak immune response, which further promotes the spread of cells beyond the endometrium. Consequently, endometriosis is known as a chronic inflammatory disease characterised by increased levels of cytokines, chemokines, and immune cells in both serum and peritoneal fluid [1].

Thus, biomarkers, which are measurable indicators of biological or pathological processes, have been carefully studied as potential tools to help in the early detection and control of diseases. However, no biomarker demonstrated sufficient sensitivity and specificity for daily clinical use due to differences in endometriosis and variability in the clinical picture [2][4]. Due to these limitations, a study of panels with several markers was conducted to determine the multifactorial nature of the disease. Inflammatory cytokines are one of the most studied important biomarkers. They control the immune system, angiogenesis, and lesion

development. Such cytokines are interleukin-6 (IL-6) and interleukin-8 (IL-8) [6]. High levels of cytokines have been found to indicate the anti-inflammatory microenvironment typical of endometriosis. In addition, there is a correlation between cytokine levels and the rate of symptom development. For instance, Perricos et al. reported that the concentrations of IL-6 and IL-8 in peritoneal fluid were significantly increased by factors of 2.13 and 2.68, respectively [7]. Additionally, Kasoha et al. demonstrated that the median IL-6 concentration in serum increased from 1.3 pg/mL to 2.9 pg/mL between the control group and patients, with a p-value of less than 0.001, indicating strong statistical significance [8].

Table 1 - The test results for the inflammatory biomarker's serum level are shown as range using Mann-Whitney-test [8].

	Control group (n = 28)	Endometriosis group (n = 59)	p-value
Hepcidin (pg/ml)	8538 (153-22755)	9534 (127-34973)	NS
suPar (ng/ml)	1.9 (1.3–3.6)	2.3 (0.8–4.2)	0.024
IL-6 (pg/ml)	1.3 (0.4-6.0)	2.9 (0.3–50.3)	<0.001
CRP (mg/ml)	1.2 (0.5–13.7)	1.1 (0.5–26.6)	NS
sTfR (mg/ml)	2.5 (1.6–4.9)	2.6 (1.9–7.2)	NS
Ferritin (ng/ml)	40.5 (8-118)	55.0 (6-194)	NS

It turns out that the levels of IL-6 and IL-8 are higher in the group with endometriosis compared to the control group, although this was mostly proven at high concentrations and at later stages. Moreover, it was pointed out that even early stages of endometriosis have an increased level of IL-6 with sensitivity around 75% and over 80% of specificity. Another study shares that levels of IL-8 are insignificant that contraject with previous research. Then, most of the studies around them are not suitable to make both interleukins are definite biomarkers since it can vary by the approach and case study [1].

In addition to inflammatory cytokines, other biomarkers are being investigated for the diagnosis of endometriosis. For example, glycoproteins such as CA-125 are one of the most studied markers; however, due to their low sensitivity, they are ineffective in diagnosis [3].

Cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) are also considered as potential biomarkers [9]. These molecules are involved in the processes of cellular interaction and tissue remodeling.

Overall biomarkers are not yet used in clinical practice, despite these advances. Changes in the phases of the menstrual cycle, lack of reproducibility between studies, and insufficient validation in large groups of patients are important problems [2]. Thus, reliable non-invasive methods for diagnosing endometriosis are still a challenge.

The lack of accurate data on the occurrence of endometriosis also adds complexity. It is mainly associated with autoimmune causes, hormone imbalance, and inflammatory mechanisms [5]. This creates the process of the appearance of lesions and their growth due to a weak immune response, which further promotes the spread of cells and their spread outside the endometrium [1].

2. 2. Current Detection Methods

Invasive methods still prevail in the diagnosis of endometriosis. In the diagnosis of endometriosis, laparoscopy with histological confirmation is the gold standard [2][5]. However, significant research has been conducted in the field of non-invasive methods for diagnosing endometriosis due to the associated risks, the high cost of these methods, and the long time interval between the onset of symptoms and diagnosis. Currently, immunological methods such as ELISA are used to identify and quantify biomarkers [10]. This is due to the high sensitivity and specificity of these methods. They can detect even minor levels of

inflammatory cytokines such as IL-6 in biological fluids such as serum, plasma, and peritoneal fluid [7].

Although ELISA methods are a reliable method of diagnosing endometriosis, they have some disadvantages. They take a long time, require multi-stage sample processing, and require special personnel and equipment [6].

In addition, imaging techniques such as transvaginal ultrasound and magnetic resonance imaging (MRI) are used in the diagnostic process. These methods are used to detect ovarian endometriomas and deep infiltrating endometriosis, but they are not as sensitive to superficial peritoneal endometriosis. However, a definitive diagnosis cannot be made using these methods [2][5].

Recently, advanced analytical techniques such as machine learning techniques have been used to improve the accuracy of the diagnostic process [4]. This was done to address the complex nature of endometriosis, as well as its heterogeneity. However, due to their high cost, their use in clinical settings has been limited.

In conclusion, modern diagnostic methods for endometriosis clearly cannot provide accurate, fast and non-invasive diagnosis. The discovery of rare biomarkers in biofluids and the study of biological changes that may result from progressive endometriosis and changes in hormones make this more obvious [1][3].

The disadvantages of existing methods highlight the need to develop alternative sensing technologies that can detect biomarkers with high sensitivity in real time. Optical biosensing technologies have demonstrated a number of advantages in this area, which makes them more effective in overcoming the disadvantages faced by modern methods of diagnosing endometriosis. Their sensitivity, miniaturisation, and the ability to detect without tags are just some of these advantages [10][11].

2. 3. Optical Biosensors

Optical sensors are increasingly attracting the attention of researchers due to their stability, good sensitivity, and cost-effective development. It has its popularity in the detection of chemical and biological components due to the possibility of using a large number of biological analytes for detection [12].

A typical fiber optic cable consists of three main layers as shown on Fig. 1. The first is a core with a diameter of up to $9\mu m$. Further around the core there is a shell with an average diameter of $125\mu m$, which ensures full reflection and propagation of light along the fiber. The most recent layer is a polymer coating, which is needed to protect the fiber and is not related to the propagation of light [13].

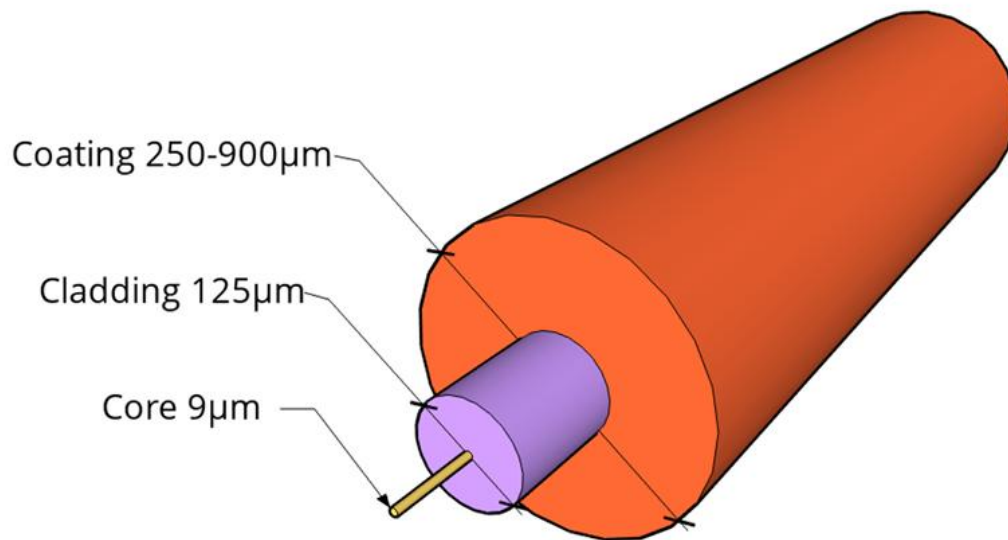


Figure 1 - Single-mode optical fiber's schema [13].

According to the core diameter, wavelength and RI difference between core and cladding it can be either single mode or multi mode. Single mode is way more effective and distribution of the optical signal is Gaussian [14].

2. 4. Optical Fiber Sensors: Principles and Types

Various types of fiber-optic sensors are used in various fields such as construction, aerospace, and medical monitoring [15]. Bragg grating fiber sensors, conical fiber sensors, plasmonic fiber sensors, and interferometric sensors are some of the most important types.

2. 4. 1. Fiber-Bragg Grating (FBG)

The refractive index of an optical fiber's core is periodically modulated to create Fiber Bragg Gratings (FBGs), which are optical sensor components. A certain wavelength known as the Bragg wavelength can be reflected while the other wavelengths in the optical spectrum are transmitted thanks to the periodic modulation of the refractive index in the optical fiber [16][17].

The following formula may be used to find the Bragg wavelength:

$$\lambda_B = 2n_{eff}\Lambda \quad [16]$$

where Λ is the grating pitch, λ_B is the resonant wavelength, and n_{eff} is the effective refractive index [16].

Quite often, Bragg-Grating is used in conjunction with other sensors due to its immunity to RI, and it can be used to detect temperature changes only and deduce sensitivity regardless of it [16]. As shown in Table 2, FBG can measure pressure, temperature, and strain [14].

Table 2 - Summary of measures and light parameters according to sensor types [14].

Sensor type	Measurand	Light parameters	Units
Cladding less	Absorption, concentration	Intensity	dB, %
Tapered	RI, absorption, concentration, pressure, temperature, strain	Wavelength shift, intensity	dB, %, nm
Interferometers	RI, absorption, concentration, pressure, temperature, strain	Intensity, wavelength shift, phase	dB, %, nm, degrees
FBG	pressure, temperature, strain	Intensity, wavelength shift	dB, %, pm
LPG	RI, absorption, concentration, pressure, temperature, strain	Intensity, wavelength shift	dB, %, nm

2. 4. 2. Tapered Fiber Sensors

Because of its great sensitivity to changes in the environment, tapered optical fiber sensors also have been employed extensively in optical sensing systems. A conventional optical fiber's diameter is reduced in a specific area to generate a tapered optical fiber. Typically, this is accomplished by carefully heating the optical fiber. There is a limited waist area in a tapered optical fiber [12] [16]. The tapered optical fiber has transition regions with a reduced diameter as it shown in Fig. 2 a, where a and c parts are transition regions of the tapered fiber. As the diameter of the optical cable shrinks, the optical mode is not adequately confined.

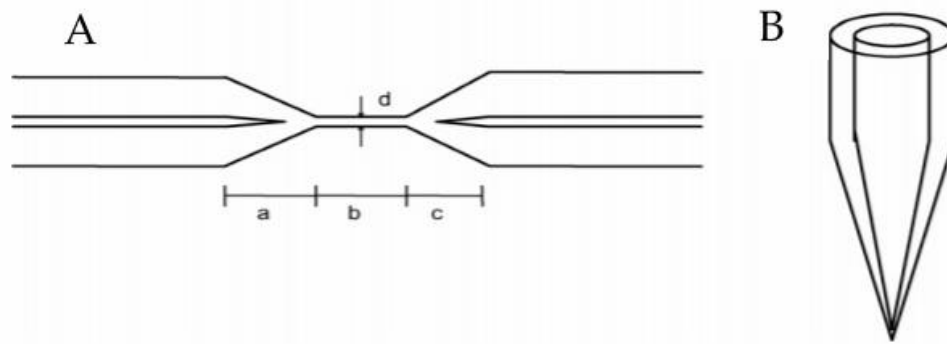


Figure 2 - Structure of Tapered Optical Fiber. a) illustration of a,c transition and b tapered parts. b) illustration of tapered tip [12].

A significant amount of optical signal propagates in an evanescent field in the surrounding medium. The exceptional sensitivity of tapered optical fibers is due to the intense interaction between the optical mode and the surrounding refractive index [16][18].

Tapered optical fibers are physically extremely sensitive to variations in the refractive index of the surrounding medium. Variations in the refractive index of the surrounding medium affect the propagation constants of guided optical modes. This is reflected in variations in the optical signal that is sent [18]. This is an undoubted advantage for sensor applications in areas requiring accurate environmental change indicators.

Sensitivity of tapered sensors is also greatly influenced by the taper geometry, particularly the waist diameter and length. As the waist diameter decreases, both the depth of penetration and the degree of contact with the organ increase. However, this also makes it more fragile and susceptible to noise and outside disturbances [12].

Additionally, multimode interference structures and Mach-Zehnder interferometers are employed in combination with tapered fibers. In applications where sensitivity is essential, such as refractive index and biochemical sensing, these devices are very successful [12][18]. However, tapered fiber devices have other problems that must be resolved in addition to sensitivity. These problems include stability and mechanical fragility. In general,

these sensors represent an optimal combination of high intensity, compactness, and versatility of RI measurement for the market. However, conical fiber optic sensors are fragile, and external interference degrades signal stability.

2. 4. 3. Surface Plasmon Resonance (SPR)

Another one of the most studied and applied methods of optical biosensing is Surface Plasmon Resonance (SPR), which is based on the use of thin films made of gold or silver creating metal-dielectric interface. Where in standard form, gold is the most preferred due to biocompatibility silver gives sharper resonance and higher sensitivity up to 2 times greater than in gold [19]. This creates collective oscillations of free electrons at the boundary.

Thus, generating a short-term electromagnetic field sensitive to external changes in the refractive index [10]. The SPR sensor's great sensitivity may be used to identify a variety of biomolecule interactions, including cytokine binding. When compared to traditional immunoassay methods, biosensors employing the SPR methodology have demonstrated quicker reaction times and IL-6 detection limits in the range up to 20 pg per mL [10].

Also, as shown in the SPR table 3, sensors can have different architectures, where each of them has its own strengths and weaknesses. For example, the angle-optimised sensor is easy to manufacture, while the prism-based SPR is notable for its stability with relatively good sensitivity [19]. However, SPR sensors with high sensitivity have their own difficulties

in the form of manufacturing difficulties, and more stable options also cannot be portable since they are quite large [10][19].

Table 3 - Different SPR architectures according to their advantages, limitations and characteristics[19].

SPR architecture	Typical sensitivity	Limit of detection	Key advantages	Main limitations
Prism-based SPR (Au film, Kretschmann)	~100–300 nm/RIU	~10 ⁻⁶ RIU	High stability, narrow resonance, reproducible kinetic analysis	Bulky optical setup, moderate sensitivity
Ag NP/GO-enhanced SPR	Up to ~890 nm/RIU	~10 ⁻⁹ M	Strong electromagnetic field enhancement, ultra-low LOD	Nanoparticle oxidation, resonance broadening, reduced long-term stability
MoS ₂ -based SPR	~431 nm/RIU	~10 ⁻⁹ M	Strong light-matter interaction, compact sensor designs	Fabrication complexity, moderate FOM
MIM waveguide-coupled SPR	>1000 nm/RIU	~10 ⁻⁷ RIU	Extreme sensitivity, strong optical confinement	Complex fabrication, high alignment sensitivity
Angle-optimized prism SPR	Target-dependent	Typically pg/mL range	Simple architecture, improved detection limits	Limited robustness, critical angular alignment
Multichannel SPR arrays	Moderate-high	pg/mL–pM	High throughput, multiplexed detection	Cross-talk, increased fluidic and data-processing complexity

2. 5. Interferometric:

Because they can identify minute changes in the environment and convert them into quantifiable data, interferometric optical fiber sensors are thought to be among the most sensitive ways to detect physical, chemical, and biological changes in the environment. The interference of two or more light waves moving in distinct directions or modes is the fundamental idea behind interferometric optical fiber sensors. Because of the consequent modification in the phase difference of these interfering light waves, every change in the environment, including variations in temperature, refractive index, and other characteristics, results in a quantifiable shift in the interference spectrum [20].

Intensity of the interference signal described as:

$$I = I_1 + I_2 + \sqrt{I_1 I_2} \cos \beta \quad [21]$$

where β is the phase difference between core mode and clad mode and expressed as:

$$\beta = \frac{2\pi \Delta n_{eff} L}{\lambda} \quad [21]$$

where Δn_{eff} as RI difference between two modes and λ wavelength of the light.

The interferometer includes several main types, such as the Michelson interferometer, the Mach-Zehnder Interferometer (MZI), the Sagnac Interferometer, and the Fabry-Perot interferometer. They are also the most sensitive methods [22].

2. 5. 1. Mach-Zehnder Interferometer (MZI)

Among them, MZI is considered the most common interferometer. It works by dividing optical radiation into two separate paths. Where one of them works as the support and another is a sensitive one. Light that goes through the sensitive one differs its propagation conditions by changing environmental conditions. This leads to the accumulation of a phase shift in relation to the supporting one. Further along the path, they recombine to form an interferometer [18]. MZI is also widely used in various fields due to its sensitivity and the possibility of sensor modification. For example, in order to additionally measure the temperature for comparison of different modified types of MZI, however, it is worth noting that their sensitivity varies greatly depending on which type of MZI is used, as shown in Table 4 [20].

Table 4 - The characteristics of different interferometric sensors [20].

Sensor	Interferometer Type	Modulated Terms	Measurand	Sensitivity
Tapered exposed-core fiber	MZI	$\gamma; \Delta n_{eff,A}$	cDNA	61.8 pm/nM
Large diameter dual-core taper	Mode Coupling	$(\partial\phi_d/\partial\lambda)^{-1}$	Temperature; Strain	572 pm/°C; −6.23 pm/μ ϵ
Microfibers MZI	MZI	$(\partial\phi_d/\partial\lambda)^{-1}$	Refractive index	44,271 nm/RIU
Thin-core fiber MZI	MZI	Δn_{eff}	Curvature	−13.53 nm/m ^{−1}
Exposed core microstructured fiber	Sagnac Interferometer	Δn_{eff}	Refractive index	−3137 nm/RIU
Dual taper-based MZI	MZI	$L_{w,A}$	Refractive index	2210.84 nm/RIU
Arc-induced tapers	MZI	$L_{w,A}$	Humidity	−0.047 nm/%RH
Polymer fiber	MZI	γ	Temperature	3.195 nm/°C
Alcohol-filled photonic crystal fiber	Birefringence Coupling	γ	Temperature	6.6 nm/°C
Polymer optical fibers MZI	MZI	α	Ultrasound	13.1 mrad/kPa
Dual-core As ₂ Se ₃ -PMMA taper	Mode Coupling	$\alpha; \Delta n_{eff}$	Temperature; Strain	−115 pm/°C; −4.21 pm/μ ϵ

2. 5. 2. Fabry-Perot interferometer (FPI)

Also, another important interferometer is the Fabry-Perot interferometer (FPI). According to their resonator configuration, these sensors can be internal and external. They differ in structure and have different manufacturing complexity, as well as stability. In the internal configuration, the sensor operates by cascading embedded mirrors along the path of light propagation inside the fiber [11].

In this way, the reflecting regions create an optical cavity where reflections create interference. One way to create it is by combining different fibers with excellent group refraction. This is how reflections appear at the boundaries forming the Fabry-Perot interferometer [11].

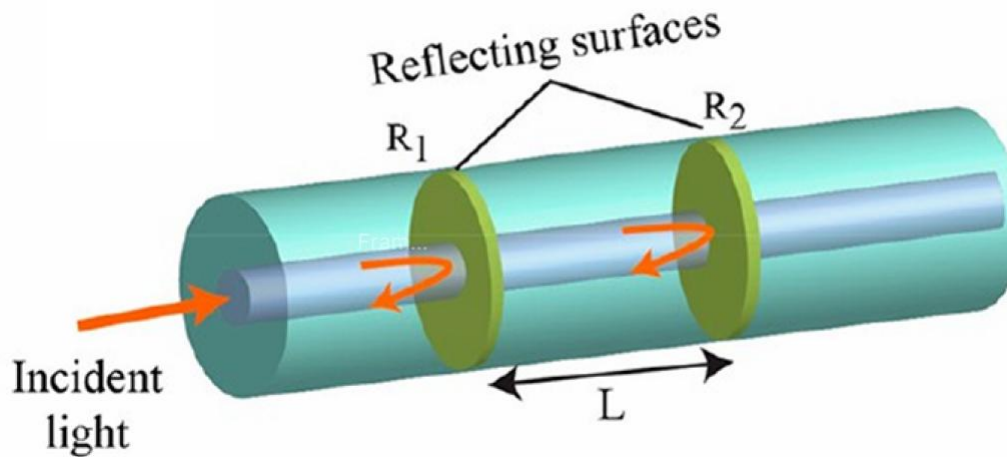


Figure 3 - Diagram of the integrated FPI sensor formed by two reflective surfaces R1 and R2 [23].

FPI and FPI-based sensors are widely used in biochemistry, including in diagnostics. For example, FPI sensors with micro resonators have a high sensitivity at LoD of about 10-25 microns. Moreover, sensors are also used in conjunction with nanomaterials that successfully detect changes in pH and glucose levels. This high sensitivity also has its limitations in the form of sensitivity to noise [23].

2. 6. Optical Fiber Biosensors for Cytokine Detection

Due to their immunity to electromagnetic interference, fiber-optic sensors can be effectively used in biomedicine. Moreover, they will also retain a sufficiently high sensitivity and specificity [17].

However, even at low concentrations, this can become a problem. It is especially difficult to identify inflammatory cytokines such as IL-6, which are generally found in bodily fluids in very small quantities as shown in Fig. 4. This calls for sensors with a high level of sensitivity, which can detect any change in their surroundings [11].

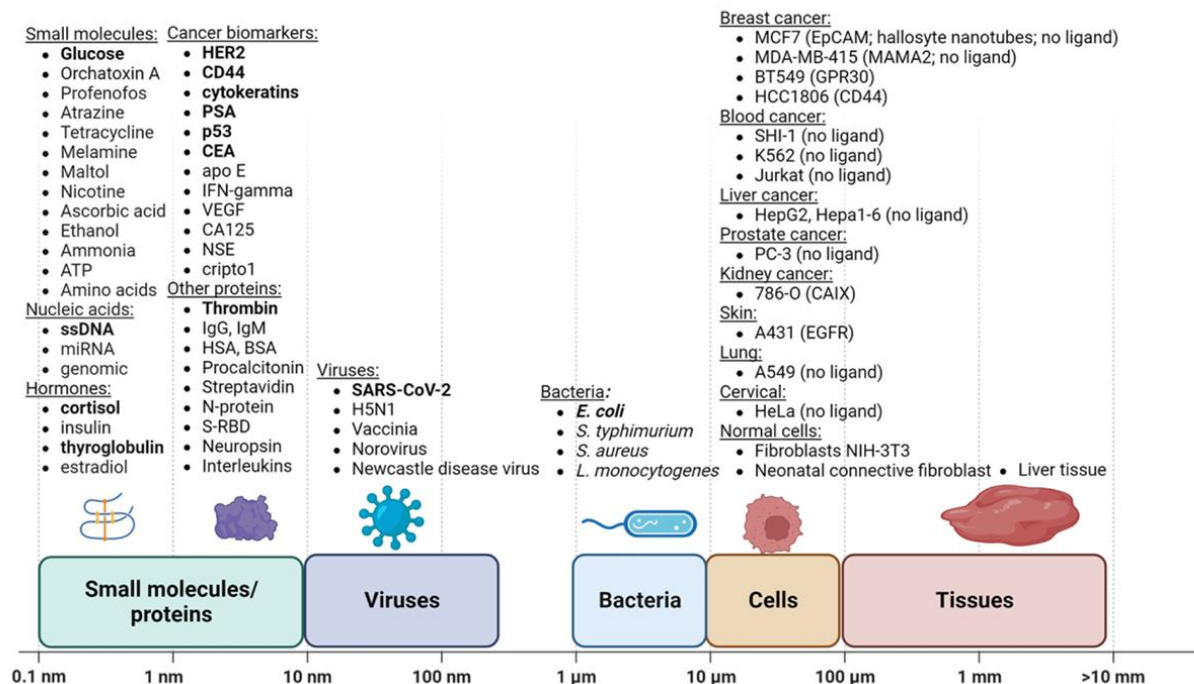


Figure 4 - Targets identified by label-free fiber optic biosensors, arranged by size [11].

One that is used for IL-6 detection is SPR biosensor. There is a lot of detection of it in the serum and plasma. For example, depending on the biosensor technology, biosensors based on surface plasmon resonance technology have demonstrated biosensing capabilities with a limit of detection as low as 1.1 pg/mL for the cytokine IL-6. Other LSPR-based

biosensors have demonstrated a serum detection limit of 11.29 pg/mL [10]. Additionally, ball resonators were used to detect IL-8 in artificial saliva with LoD 0,91 fM with a wide range of detection. Moreover, the selectivity of the biosensor has been verified by comparing it with other non-target proteins [24].

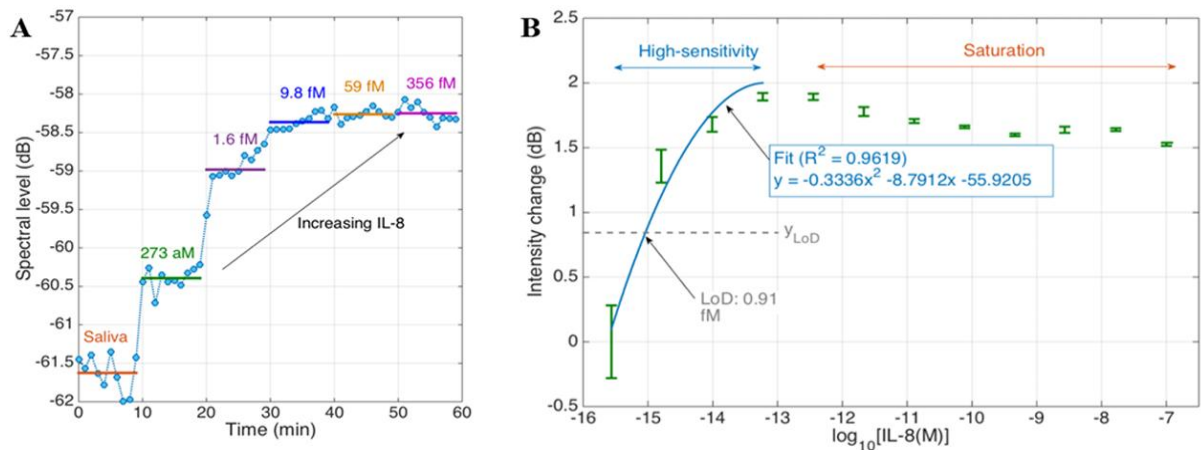


Figure 5 - IL-8 detection with a ball resonator. A) Sensogram for spectral level with different concentration for the sensor diameter of 556 μm . B) Sensitivity of the BR sensor over a wide range of IL-8 concentrations [24].

The SDI biosensor also showed high sensitivity for cytokine detection in artificial saliva, reaching 480 aM and 23.4 fM for IL-6 and IL-8 respectively. However, it has a low stability, changing every time, and the sensor also reacts out of proportion to the concentration, which can give inaccurate data [25]. This means that noise, environmental changes, and uncertainty of the system influence the sensor. Therefore, it is required to increase the level of reliability of the signal. In other words, it is required to develop methods of noise reduction and signal processing in order to correctly recognize cytokines in small amounts. The signal is very sensitive to external influences. Therefore, it is very important in interferometric sensors [25].

2. 7. Noise, Stability and Signal Enhancement

For fiber-optic sensors, the signal-to-noise ratio is important when deciding on sensor operability. Due to their structure, interference will need to be considered when using these sensors, as noise has a big influence on the signal's accuracy [26]. The precision of the signal can be impacted by even little changes brought on by temperature variations, mechanical vibration, or polarization. Furthermore, when detecting low quantities of biomarkers, the signal's accuracy may be impaired [27][28].

The signal level is similar to the noise level when biosensors are used practically to analyze various cytokines, such as IL-6, IL-8, etc. Therefore, increasing the signal-to-noise ratio requires noise characterisation [29]. Various signal analysis techniques have been created to overcome these problems. For instance, frequency domain analysis, time domain signal stability analysis, and filtering methods have been introduced [27][30].

2.7. 1. The Allan variance

The Allan dispersion has gained significant importance in the analysis of noise in time-dependent signal processing. Allan's variance assesses the variations between subsequent averaged data, offering a more trustworthy depiction of stochastic noise processes than conventional variance, which is highly susceptible to long-term deviation [31].

Allan variance defined as:

$$\sigma^2(\tau) = \frac{1}{2} \langle (\underline{y}_{m+1} - \underline{y}_m)^2 \rangle \quad [31]$$

where y_m is the signal averaged over a time interval τ . This form can be used to investigate the stability of the signal as a function of the averaging time.

Plotting the Allan deviation $\sigma(\tau)$ on a log-log scale allows for the differentiation of various forms of noise based on the curve's slope. As it is illustrated in figure 6, white noise is

displayed by linear dependence with the slope $-\frac{1}{2}$. Where white noise can be reduced by rose averaging time [31].

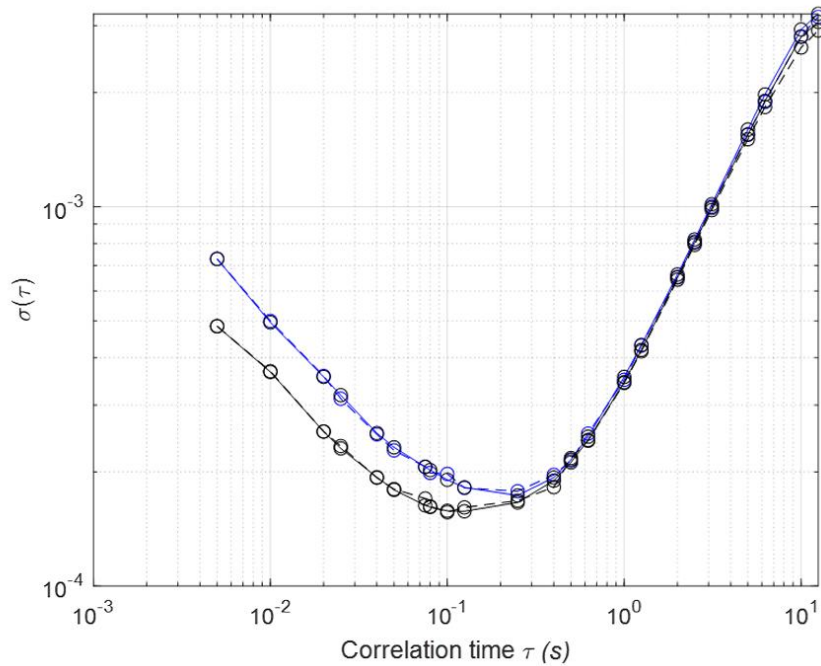


Figure 6 - Logarithmic plot of Allan Deviation for non-overlapping (dashed) and overlapping (solid) estimators for two polymers [31].

There are several sources of noise for an optical fiber biosensor, such as phase instability, ambient noise, and polarization noise. These effects may be measured and various noise sources, such as random walk noise and white noise, can be differentiated using the Allan variance approach [31].

2. 7. 2. Kalman Filtering

Although Allan's variance allows for an effective classification of noise sources, it also does not reduce their effect on the signal. Therefore, Kalman filtering is also used as one of the most common methods of signal estimation to reduce noise levels. The accuracy of the measurement signal in refractive index measuring methods like interferometric and resonant

biosensors is strongly influenced by noise from light sources, ambient noise, and electronic detector noise. To improve signal stability and reduce LoD, new signal processing methods must be used [32].

The Kalman filter is a recursive estimating strategy that blends previous system information with current measurements, in contrast to other signal estimation techniques like curve fitting methods that involve separate prediction of resonance for each data point. This lowers estimated errors by enabling real-time system state monitoring [32].

A state-space model serves as the foundation for the Kalman filter. One way to characterize the dynamics of the system is:

$$x_{k+1} = Ax_k + \omega_k \quad [32]$$

where x_k is the state vector, A is a transition matrix, and ω_k is a process noise.

And measurement model is:

$$z_k = h(x_k) + v_k \quad [32]$$

where z_k and v_k are measured signal and measurement noise respectively.

Then, the state is iteratively updated using the forecasting and correction scheme:

$$\hat{x}_k = \hat{x}_{\underline{k}} + G(z_k - \hat{x}_{\underline{k}}) \quad [32]$$

where G_k stands for Kalman gain.

In the study, it was found that the use of Kalman filtering leads to a decrease in noise deviation of 2-3 compared to traditional methods and, subsequently, an enhancement of the detection limit. For example, in protein binding the extended Kalman filter projection (EKFP) method improved LoD from 10 pg/mL to 1 pg/mL [32].

2. 7. 3. Butterworth filter

Another widely used method that suppresses high-frequency interference is the Butterworth filter. This low-pass filter lets you preserve a useful signal while removing high-frequency interference.

This filtering method is often used in optical systems, enabling flat-band operation while reducing LoD [33]. For this, the 5th order is usually used with a normalized cutoff frequency of 0.05 [34].

However, the fiber's data must also be taken into account. For example, an erbium-doped filter enhances its performance with increased fiber length [33].

2. 8. Research Trends

At the moment, optical sensor technology is increasing in price and attracting the attention of researchers. Currently, the main optical sensors in the market are bragg-grating sensors, raman scattering, interferometric. It is worth noting that according to Fig. 7 interferometers began to gain popularity only in the last 10 years, having previously remained unpopular [13].

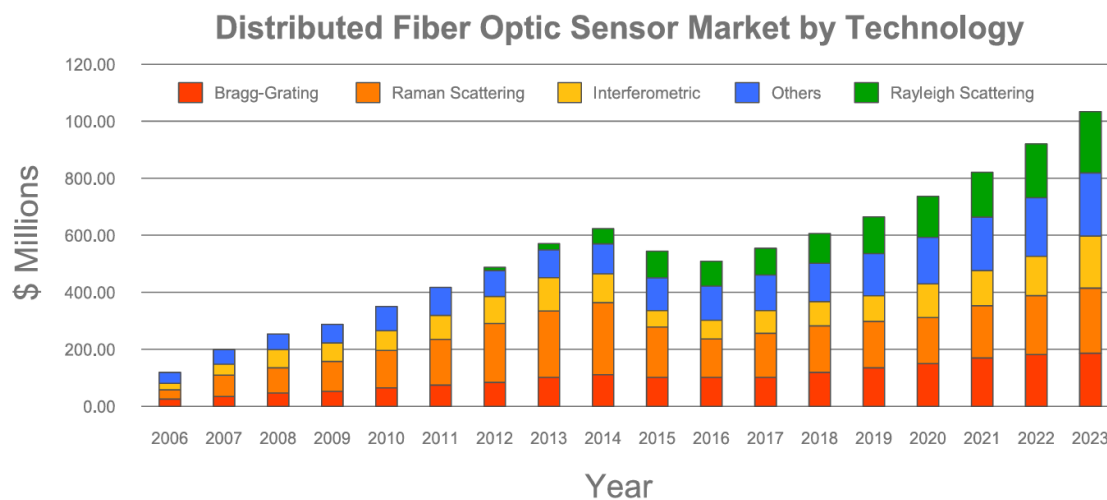


Figure 7 - Optical Sensors in Technological Market order by year [13].

3. METHODOLOGY

3. 1. Sensor fabrication

Two types of fiber optic cables are used to create SDI sensors. One of them is SMF-28 with a 1550 nm wavelength, which in this case comes with an FC/APC pigtail, and the second is a fiber with improved backscattering (EBF). Where EBF is used to increase intensity, making the sensor particularly sensitive. To obtain an SDI sensor, the splice-and-cleave method is used.

Subsequently, both optical fibers are first subjected to the removal of the protective layer. Further, to improve the connection, their ends are cut using a high-precision fiber-optic jib (Fujikura CT-08). After that, the Fujikura 12-S connects them. This creates a partially reflective surface that acts as one of the reflective borders. It is also important to note how well it went, as sometimes they are soldered with large defects.

After bringing them together with the same Fujikura CT-08, the remaining length is removed from the EBF side, leaving only a small length (approximately 500 micrometers) for sensitivity. A segment that is too large will also work in the opposite direction, reducing sensitivity. As a result, the necessary SDI sensors are released. With this approach, it is impossible to obtain completely identical sensors due to differences in sensitive segment length, potential damage, and improper soldering. Still, they can always be sorted, and the most effective ones can be taken.

3. 2. Sensor Calibration

After manufacturing, the sensors are calibrated in order to select sensors suitable for future use based on sensitivity to environmental changes. A sucrose solution in various concentrations was used as a calibration medium, which indicates whether the sensors have a perception of RI.

Since only a small amount of the solution is needed, a 40% sucrose solution is initially prepared for easier use. Further, other concentrations are created on its basis. The first concentration comes from diluting 1.5ml of a 40% solution to 4.5ml of water to obtain a 10% solution in an amount of 6 ml.

Other concentrations are obtained by adding 150 mcl of 40% sucrose solution to the existing solution until 6 different concentrations are reached as it is shown in Table 5.

Table 5 - Concentrations for sensor calibration with all the components and overall volume

№ of concentration	Concentration percent	Sugar	Water (ml)	Volume (ml)
1	10%	0.6	5.4	6.00
2	10.73%	0.66	5.49	6.15
3	11.43%	0.72	5.58	6.30
4	12.09%	0.78	5.67	6.45
5	12.73%	0.84	5.76	6.60
6	13.33%	0.9	5.85	6.75

Further, there were three measurements for each concentration, in order to further work with the average value. Then the most suitable sensors with high sensitivity were determined based on spectral peaks and troughs.

3. 3. Functionalization

Before using fiber-optic sensors for biomolecule detection, they undergo a functionalization process. The functionalization of the sensor surface takes place in several stages.

At the beginning, the sensors' surfaces are cleaned by immersing them in a piranha solution for 15 minutes. This solution consists of sulfuric acid and hydrogen peroxide in a 4:1 ratio and is a fairly powerful cleaning agent that requires caution due to its high corrosivity. It doesn't take much to clean it, just 2ml.

After the sensors are cleaned of possible organic components, the silanization process follows. The sensors are immersed in a solution with 1% APTMS in methanol for 20 minutes. With this treatment, a reactive layer is formed on the surface, suitable for further attachment. For this, the sensors are also heated in an oven for an hour at 110 degrees Celsius, which makes the layer more stable and its adhesion stronger.

Then, after another rinse of the sensors, they are immersed in a PBS:GA solution (1:1) for 1 hour in a shaker. This maximizes crosslinking with the amino groups of molecules. This is followed by incubation with a concentration of antibodies (2 mcr of antibodies per 498 mcr of PBS) for an hour, which should yield a layer of immobilized antibodies that selectively binds a specific analyte.

After incubation, the sensors are immersed in a 1% mPEG solution in PBS for 30 minutes, which blocks the remaining active centers. This is the final step in the functionalization, after which the biosensors are stored in the refrigerator (-4 degrees Celsius) for further use.

It is precisely because of functionalization that sensors respond to specific antibodies, so incorrect functionalization can lead to incorrect results or a non-functioning sensor. One of

the main problems is the fragility of the sensors, which can lead to broken functionalized ends.

3. 4. Signal Processing

The last one is signal processing. To do this, all sensors are immersed in a solution with antibodies with different concentrations after functionalization. In this case, these are 6 concentrations, where each of them has 20 recordings with an interval of one minute. This approach helped to determine the dynamics of the signal and also its stability. After that, the signal is processed through python, where the main goal is to reduce noise and improve the signal.

To begin with, a Butterworth filter is applied to each spectrum in order to remove high-quality noise, and only after that the values are averaged for analysis, and the two extreme regions of the spectrum are trimmed in order to eliminate a large amount of noise.

Subsequently, the peaks and troughs in the spectrum are identified as the maximum and minimum values of the interference signal, respectively. Determining the precise positions of these features, rather than relying on discrete values, reduces the influence of noise. The most stable spectra are then selected using the coefficient of determination.

The peaks and troughs observed in the spectrum correspond to the maxima and minima of the interference signal. A low-resolution estimate is subsequently applied to mitigate the impact of noise. The most stable spectra are selected for analysis based on the coefficient of determination (R^2).

During the experiment, the position of a pre-selected depression is determined for each spectrum to construct a time series corresponding to each analyte concentration. Next, the time series are analyzed through three approaches, where one is completely unprocessed, the

other is filtered, and the last is with a Kalman filter. And for each one, the standard deviation, the average wavelength, and so on are calculated.

4. RESULTS

4. 1. Calibration

The first part of the sample consists of calibrated sensors. All sensors were soaked in sucrose solution with different concentrations and refractive index between 1.3476 and 1.3584.

Initially, 33 sensors were used, of which only 14 were stable enough to be selected for further study. Among them: sensors 1 and 2 from the first calibration, 1, 4, and 6 from the second, 1, 4, 5, 6 from the third, 2, 4, 6 sensors from 4 and 4th sensor from 5 calibrations. As can be seen in Table 6, only some of the sensors showed a stable and satisfactory response to calibrations and changes in RI. In particular, sensors with a sensitivity above 60nm/RIU were selected, but more information will be provided later on how sensitivity is not a guarantee of a good sensor and its stable operation.

Table 6 - Sensitivity from calibration stage.

Calibration #	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5	Sensor 6	Sensor 7	Sensor 8
1	no sensitivity	no sensitivity	no sensitivity	no sensitivity	102.38	no sensitivity	no sensitivity	no sensitivity
2	69.61	no sensitivity	17.21	108.77	2.47	no sensitivity	-	-
3	64.80	no sensitivity	no sensitivity	14.49		211.28	no sensitivity	no sensitivity
4	no sensitivity	165.64	no sensitivity	130.27	no sensitivity	129.31	-	-
5	no sensitivity	21.38	no sensitivity	25.70	no sensitivity	-	-	-

And if we look at those who are more stable, then most of them showed a steady change with a change in concentration, which shows the sensitivity of the sensors. However,

sensors with high sensitivity are not always suitable for further use. For example, the first sensor showed a clear wave shift when the refractive index changes and has a high linearity ($R^2 = 0.9007$). However, its sensitivity is -116.95 nm/RIU as indicated in Fig. 9.

In contrast, the second sensor seemed very sensitive, but had poor linearity ($R^2 = 0.6736$). As shown in Fig. 10, the spectral characteristics do differ for different concentrations, while in the first sensor spectral with different concentrations overlapping in Fig. 8.

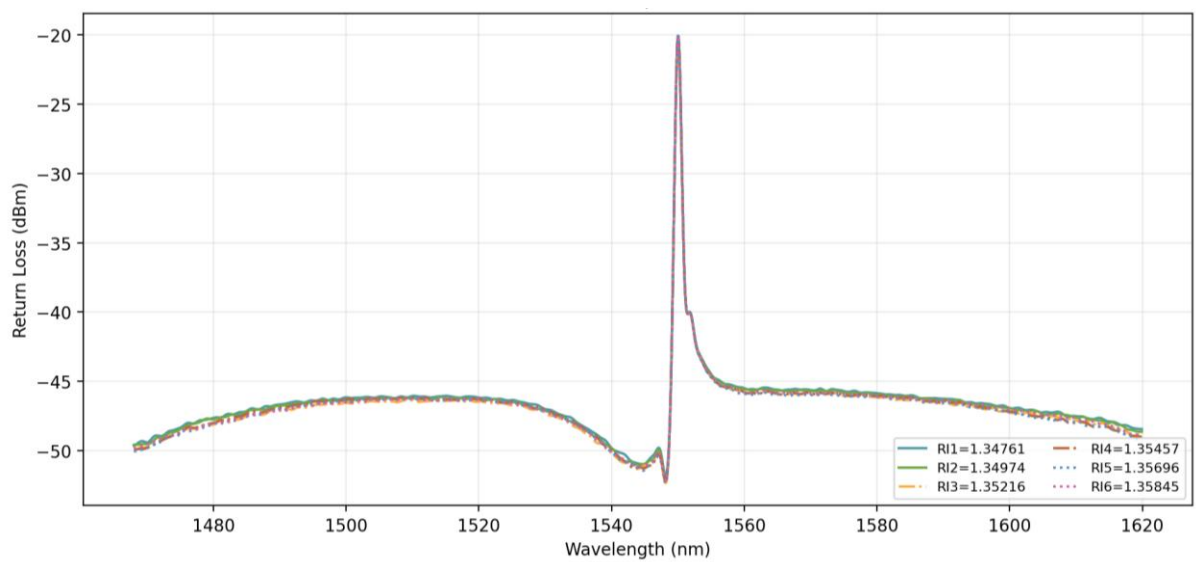


Figure 8 - Spectral of the first sensor with 6 different concentrations.

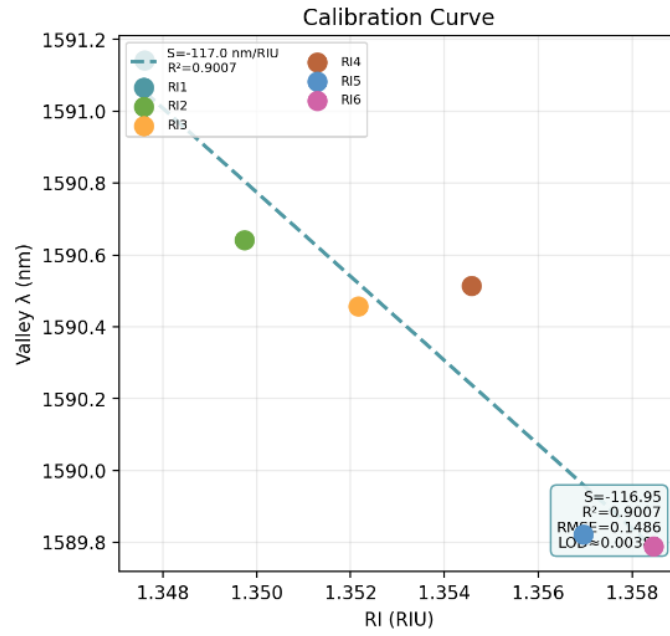


Figure 9 - Calibration curve of the first sensor with 6 different concentrations.

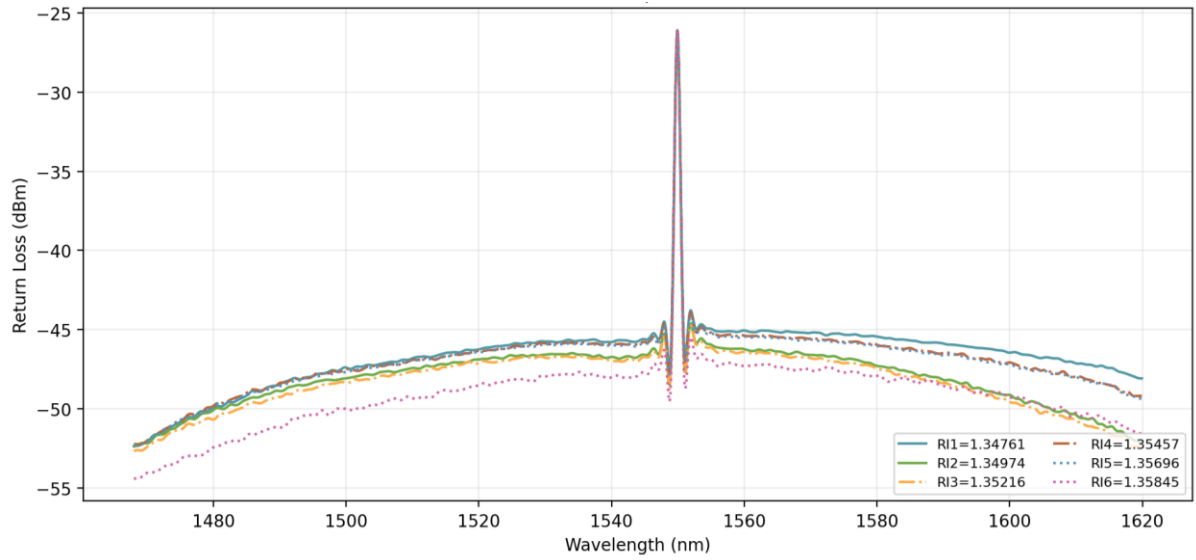


Figure 10 - Spectral of the second sensor with 6 different concentrations.

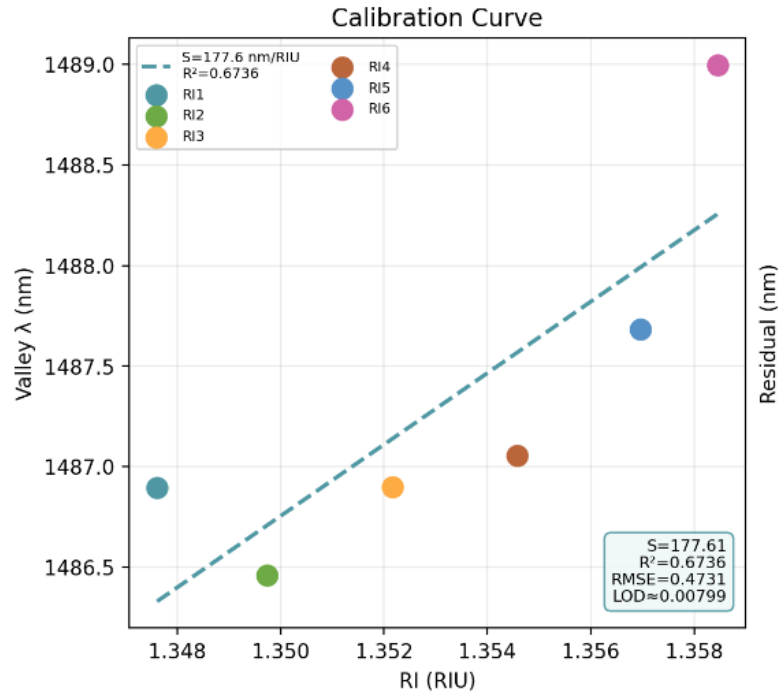


Figure 11 - Calibration curve of the second sensor with 6 different concentrations.

Sensitivity, which is independent of the calibration curve, must also be considered. The sensor exhibits a low R^2 of 0.6754. While sensitivity remains high with being 133.42 nm/RIU in Fig. 12a.

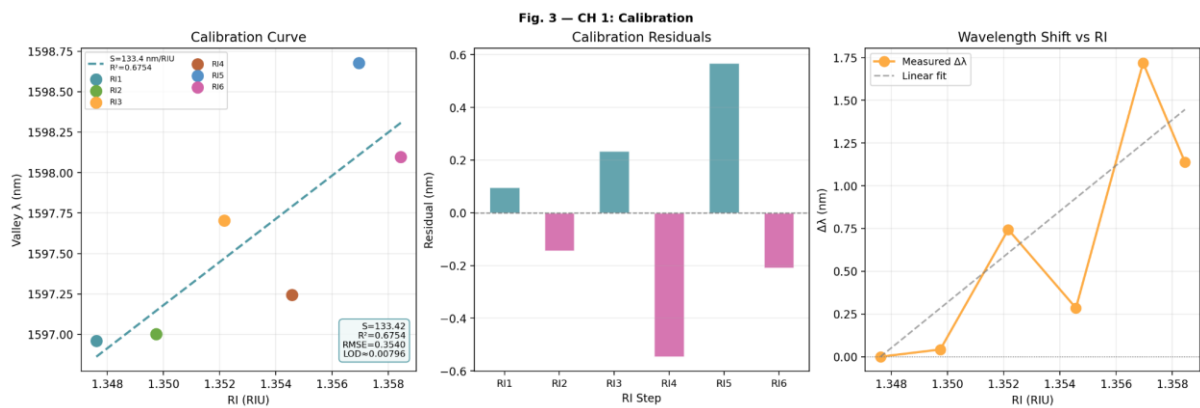


Figure 12 - Results from Calibration 2 for Sensor # 1 from a) Calibration curve, b) linear regression results, c) Wavelength shift as a function of RI.

It is also worth mentioning how the original signals had broadband noise in the entire frequency range. Due to filtering, the noise is reduced by suppressing the high-frequency components as shown in Fig. 13. However, it is worth noting that noise also includes possible important data.

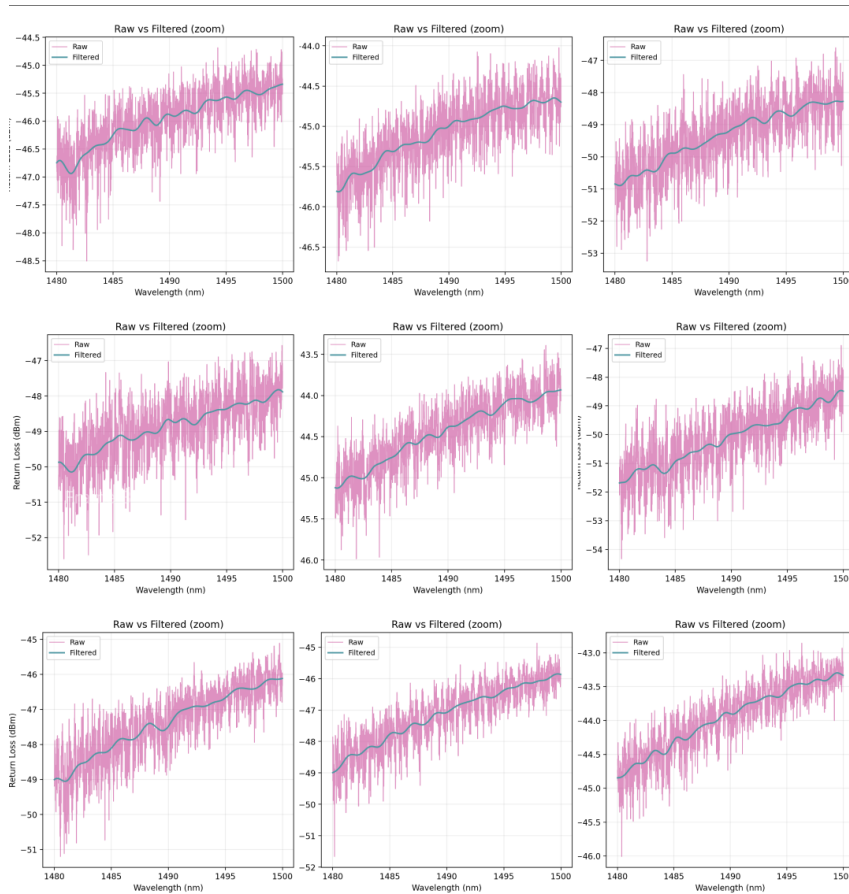


Figure 13 - Visual representation of the reduced noise for each sensor.

4. 2. Detection

For detection the 8 sensors that partially passed the calibration were chosen. For detection 6 concentrations were chosen that would be antibody solution diluted in PBS adding it each time in the amount of 2700mcr. And per each concentration it was 20 repeated measurements that were taken with 1 minute interval.

For detection method several signal-processing methods were evaluated which includes Butterworth filtering, wavelet transform, Savitzky–Golay baseline, and two types of Kalman filtering (Kalman-1D and extended Kalman filter) baseline correction.

In the detection curves, both sensors show how the noise increases the signal shift from a change in RI. However, the Kalman methods in the first sensor in Fig. 14 have the most stable slope, where an increase in concentration increases the signal. However, even so, the dependence is very much dependent on noise, but the Savitzky–Golay baseline, on the contrary, has a negative slope, which is fundamentally different from the rest. This anomaly may indicate the removal of useful signals at the same time as noise.

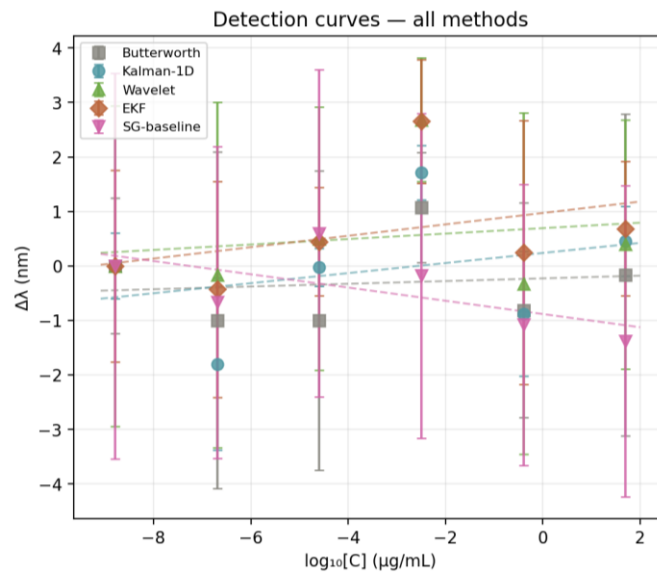


Figure 14 – Detection Curves for all signal processing methods for Sensor 1.

The same is observed with sensor number 4, which is illustrated in Fig. 15, however, unlike the first sensor, all values are close to 0, so there is no such dependence in it as in the first sensor.

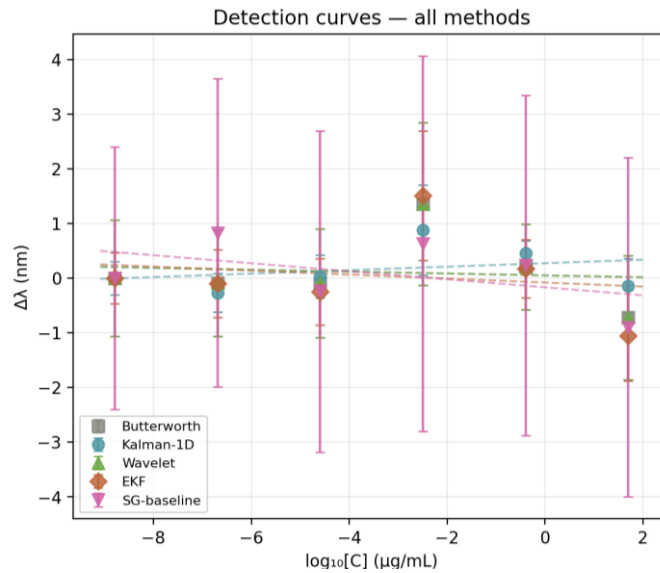


Figure 15 - Detection Curves for all signal processing methods for Sensor 4.

Also, R^2 is low for both signals with all signal processing methods. As shown in Fig. 16 The Savitzky–Golay baseline has the highest linearity value, but it does not reflect a real improvement in signal quality, as it demonstrated abnormal behavior. Further, again, the Kalman-1D extended Kalman filtering methods show relatively good results, but the values are worse than in the SG baseline. However, they also have the usual dynamics of signal variation.

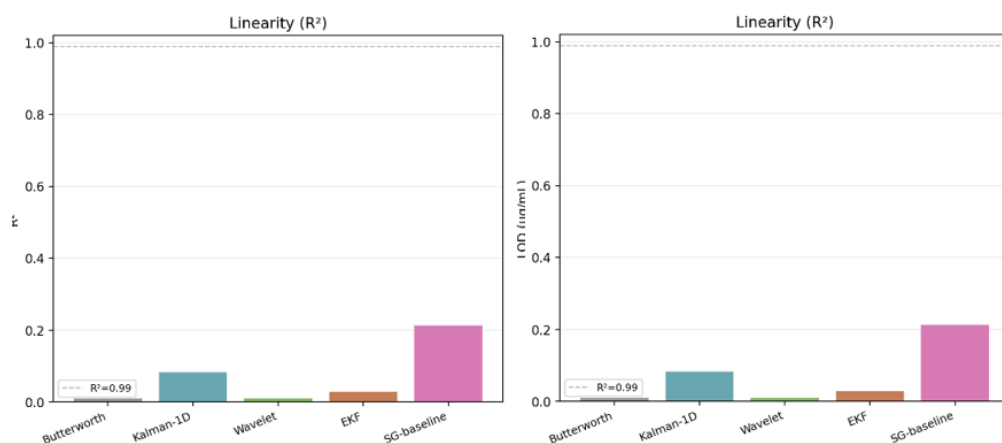


Figure 16 - Linearity for both sensors for all signal processing methods.

Further, when comparing the LoD, differences between the two sensors were revealed. For sensor 1, Kalman-1D stood out with the lowest value with 26 mcrg/ml, which means an improvement of 3.5 times than with the raw signal in Fig. 17.

Further, extended Kalman filtering showed a more impressive result, which was approximately 40-45 mcrg/ml. Butterworth, on the other hand, led to an increase in the detection limit, which was since smoothing the spectrum led to a decrease in calibration dependence. But in another sensor from Fig. 18, the LoD level of the wavelet is the same as through Butterworth filtering, which is different from what was in the first sensor.

It can be seen how Kalman's methods are among the most effective for reducing the detection limit.

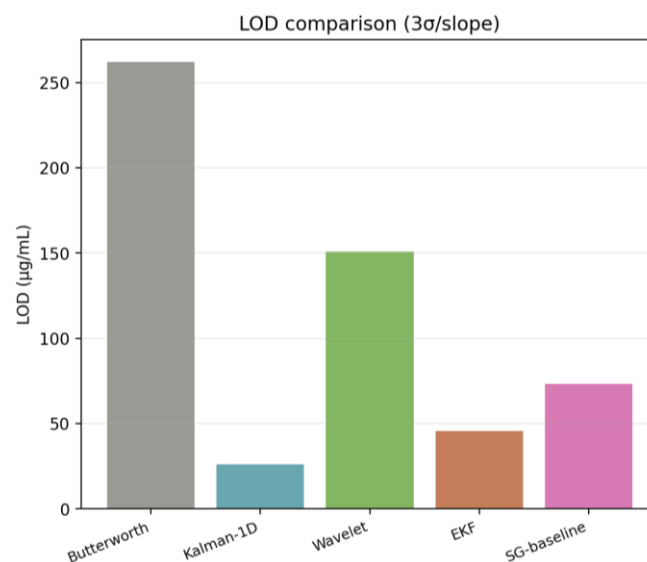


Figure 17 - LoD comparison by several signal processing methods for Sensor 1.

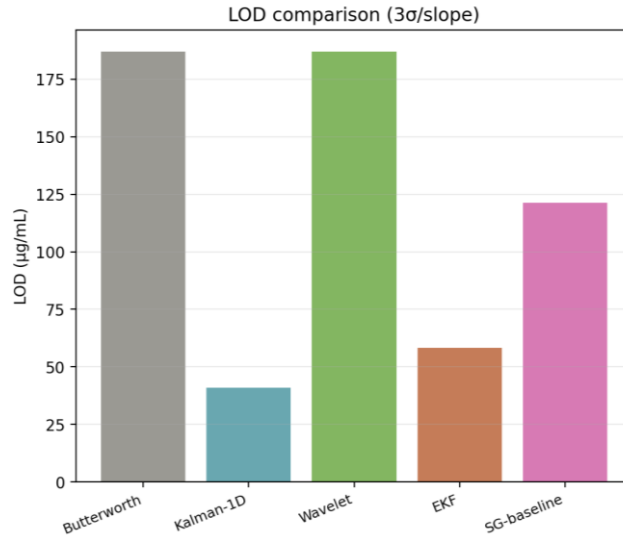


Figure 18 - LoD comparison by several signal processing methods for Sensor 4.

Through RMSE analysis, it can be found out that the SG-baseline has the smallest values due to a linearly smoothed approximation with values of 0.5 for both sensors. Butterworth also has small values for a similar reason, with values of ~0.75 and ~0.6 for the first and fourth sensors, respectively.

Also, it is worth noting that the Kalman-1 value for the fourth sensor is much lower than for the first one. However, both Kalman filterings generally have higher values for both sensors due to the steeper slope of the calibration curves.

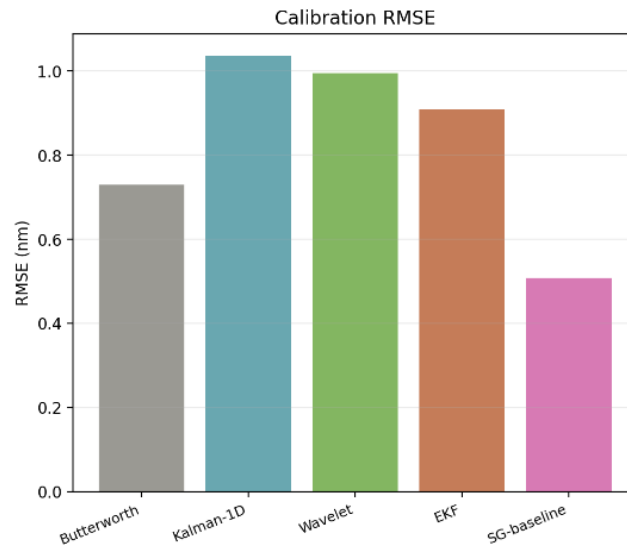


Figure 19 - RMSE comparison if different signal processing methods for sensor 1.

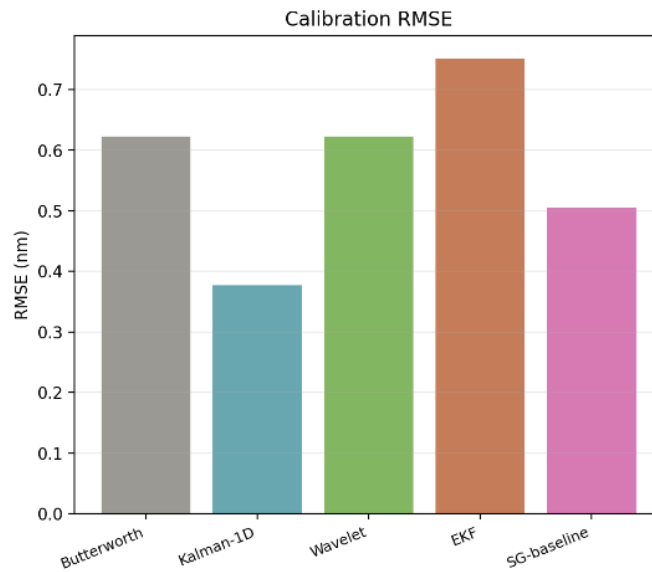


Figure 20 - RMSE comparison if different signal processing methods for sensor 4.

Further evaluating the repeatability for both sensors can be seen as in Fig. 21

Kalman's method shows the lowest values among all, while SG-baseline, on the contrary, with the highest values, shows the worst repeatability. In general, you can see how such a correction with Butterworth, SG-baseline, on the contrary, worsens the values. Also, turning to sensitivity analysis, it turns out that Kalman's methods have the highest sensitivity,

excluding SG-baseline for lack of value. Similar results are found for the fourth sensor in Fig.

22.

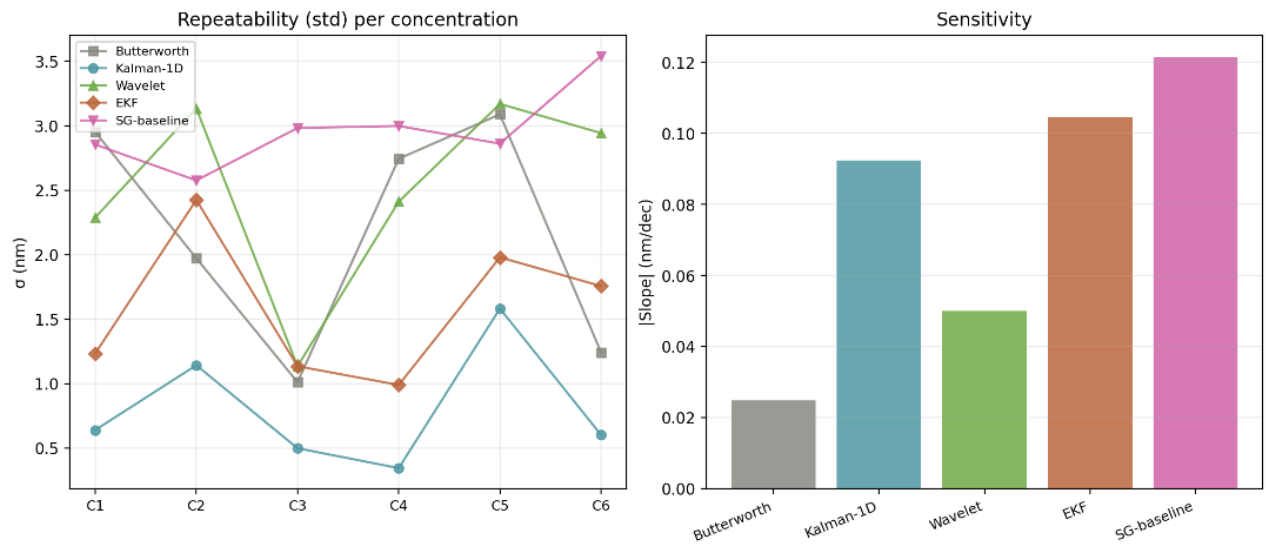


Figure 21 - Comparison of repeatability and sensitivity across signal processing methods for Sensor 1.

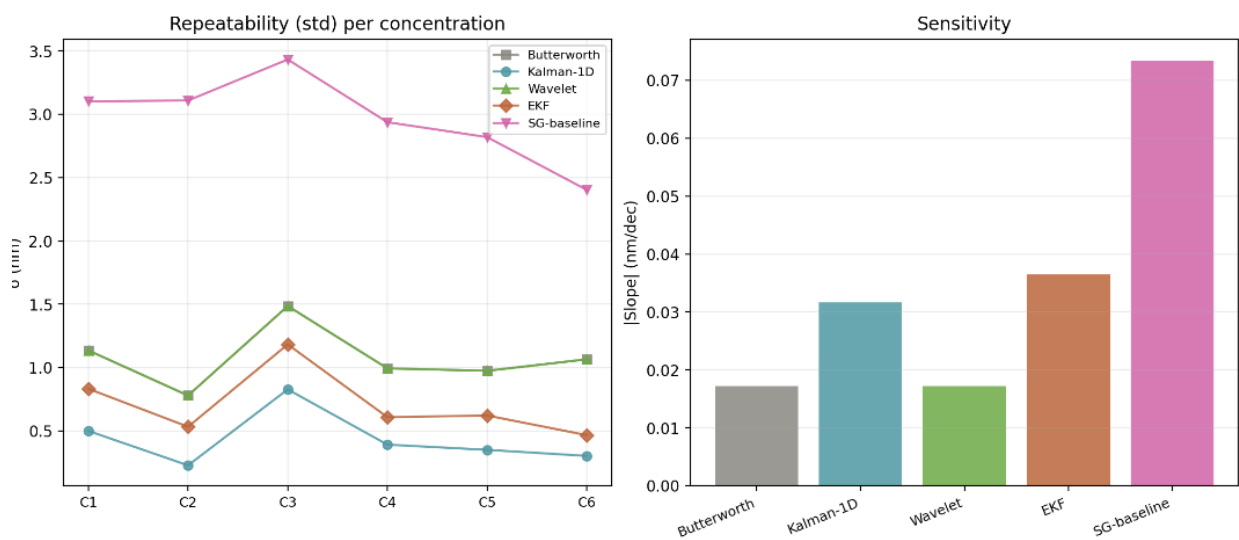


Figure 22 - Comparison of repeatability and sensitivity across signal processing methods for Sensor 4.

The signal-to-noise ratio (SNR) for each sensor was estimated using the Median Absolute Deviation method. Thus, an unstable signal can be observed in the greenhouse map for the first sensor. Especially concentrations 2 and 3, where low signal-to-noise ratios are

often found. The third concentration in both sensors as a whole has a low SNR (15 for the first and 25 for the second) what can be seen in Fig. 23-24. Since the deterioration occurs in mid-range concentrations, the problem may be related not only to the signal quality itself, but also to other factors.

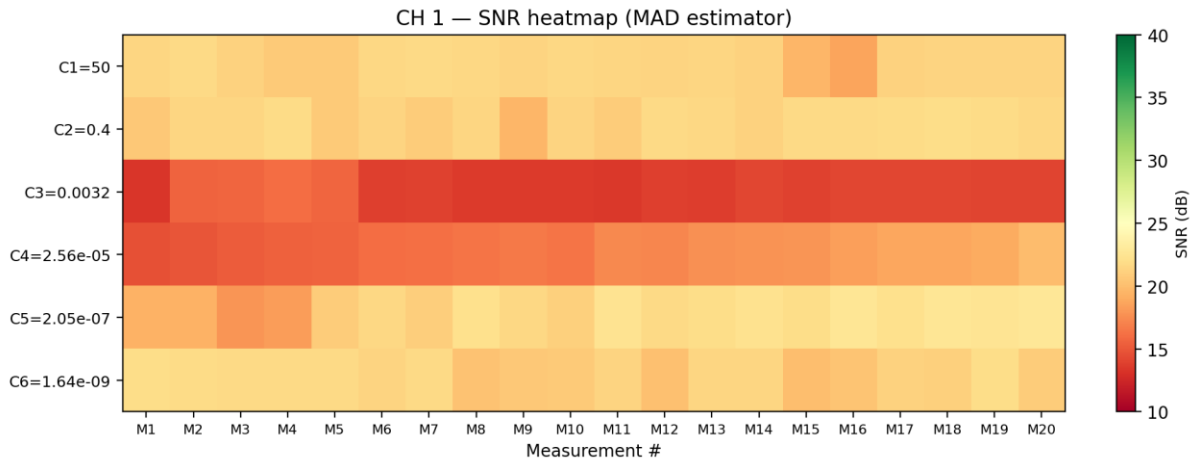


Figure 23 - Signal-to-Noise Ratio heatmap for Sensor 1.

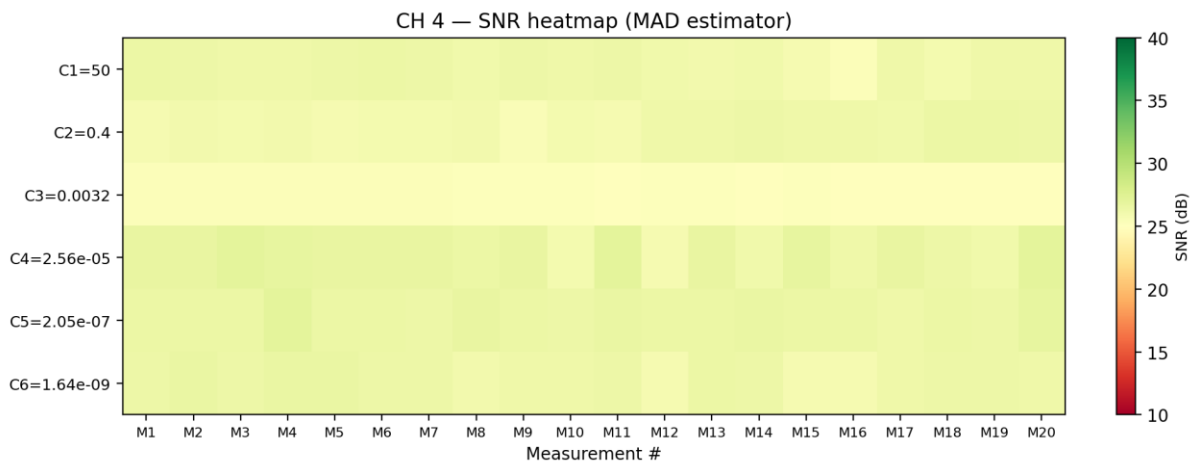


Figure 24 - Signal-to-Noise Ratio heatmap for Sensor 4.

Allan deviation was used to estimate the change in noise level during signal averaging. Slow noises prevail here, which are not suppressed by simple averaging, as can be seen from the Butterworth and Wavelet methods in Fig. 25. The Kalman-1D method already shows better results, although the increase in σ with an increase in τ shows a noticeable

decrease in slow noise. Extended Kalman filtering has the same tendency, but with a higher σ than Kalman-1D.

The fourth sensor shows greater stability, where the curves are more regular. Again, the Kalman-1D method has the best results, as well as extended Kalman filtering. When like a Wavelet next to them, it is less noticeable, which indicates the preservation of low-frequency noise. Also, at low concentrations, it turns out that at lower τ , σ decreases, and at higher τ , there is an increase.

In general, of all the methods, the Kalman method is the most effective when Butterworth could, on the contrary, degrade the signal along with the Wavelet, SG-baseline.

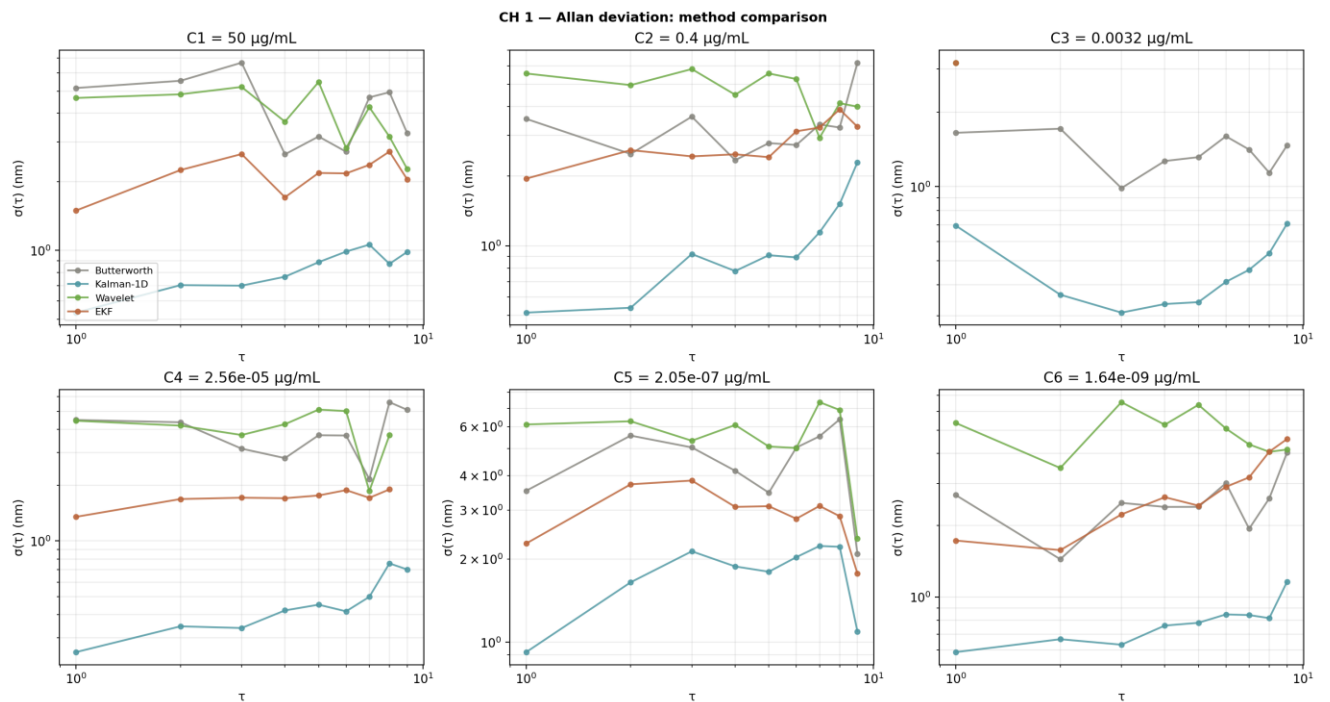


Figure 25 - Allan Deviation comparison across several signal processing methods for Sensor

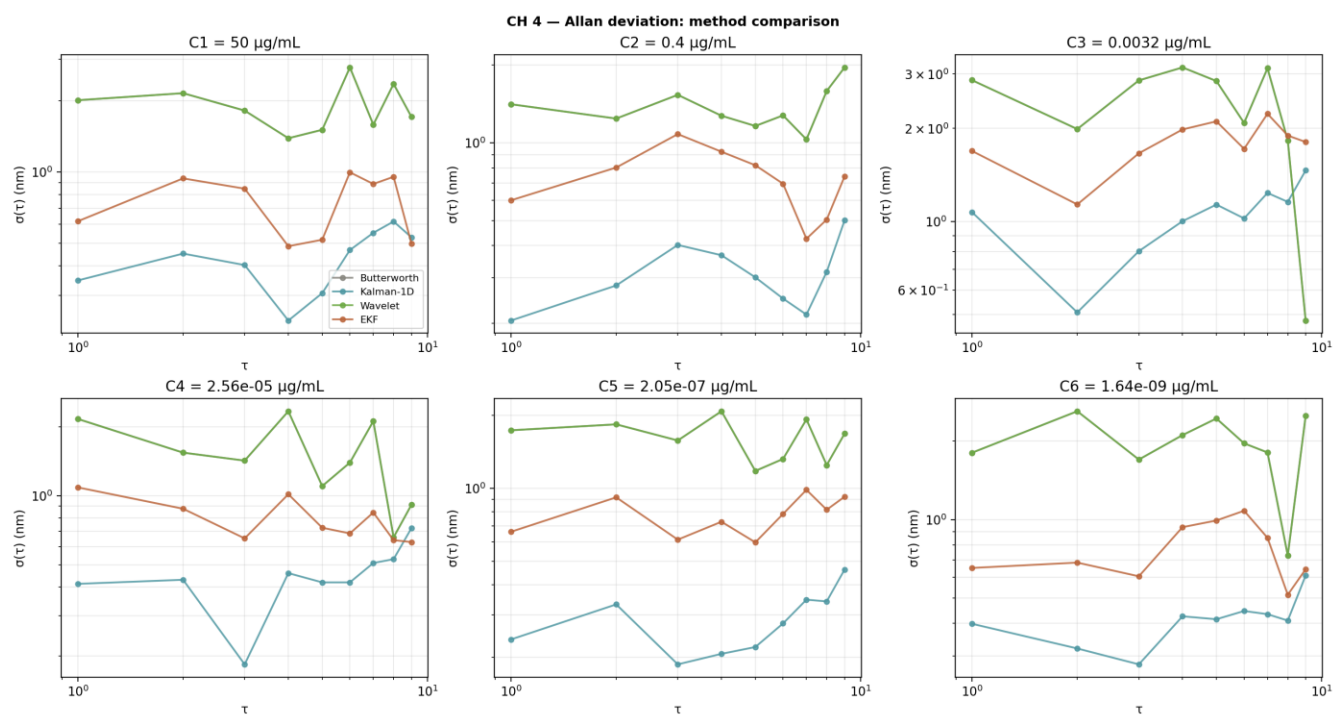


Figure 26 - Allan Deviation comparison across several signal processing methods for Sensor

5. CONCLUSION

To determine the minimum concentrations and determine the refractive index, the effectiveness of distributed interferometric fiber-optic sensors (SDI) was evaluated. During calibration, the results showed a very low percentage of sensors that actually pass the sensitivity test. It was the same in the detection. This may be due to several reasons, such as the fragility of the sensors themselves, defects, and also poorly connected analogues. These reasons cannot be seen with the naked eye. Therefore, incorrect sensor operation can only be visible after all the steps have been performed.

Calibration results confirmed that SDI sensors detect refractive index changes through measurable wavelength shifts. However, significant performance differences were observed between channels. Some sensors demonstrated low sensitivity despite adequate linearity, while others exhibited high sensitivity but poor stability, and a subset showed strong linearity with intermediate sensitivity. These findings indicate that comprehensive evaluation of sensor performance should consider sensitivity, linearity, and noise characteristics rather than relying on a single metric.

However, it was found that spectral troughs provide greater stability and sensitivity than their peaks. In addition, sensors that showed high sensitivity had poor linearity and vice versa. It turns out that only one sensitivity is not enough to characterize the sensor. Sensors also receive a lot of noise, and some of them are just the ones that can be useful for detection. Moreover, through the analysis of variance, it was clear that white noise prevails in the short-term averaging of the signal, and in the other case it is low-frequency noise.

Also, by using Kalman filtering, you can get less noise, but also preserve the signal and increase the LoD, when Butterworth's method only worsened everything. This means that you also need to monitor how much noise is removed and whether it will negatively affect the sensitivity of the sensors.

In conclusion, the performance of optical fiber sensors is regulated through complex interactions between sensitivity, linearity, and noise. Then to get the effective sensing method could be achieved by a complex work perfecting the balance between the fabrication, functionalization, noise cancelation.

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