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3 **Photonic sensor to detect rapid changes in CRP levels**

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## 30 **Abstract**

31 One of the most important biomarkers used to determine inflammation is C-reactive protein  
32 (CRP). Its level, when it is within the range that does not define inflammation, informs about  
33 the risk of cardiovascular events. If the norm is exceeded and inflammation is detected in the  
34 body, CRP level can increase 1000 times within a few hours. The type of infection can also be  
35 determined based on the level of elevated CRP. All this makes CRP a very important element  
36 of diagnostics.

37 A sensor based on low coherence interference is presented. Preliminary studies have shown  
38 that its sensitivity is 5.65  $\mu\text{g/L}$  and the measurement time is short,  $< 10$  minutes. The entire  
39 system is built of commercially available components, which allow production cost  
40 minimalization. In addition, the user-friendly operation allows it to be operated by unqualified  
41 people. Due to these features, our solution is a promising alternative to commercially used  
42 ELISA, which needs trained personnel to perform time-consuming measurement procedures.

43 Keywords: biomarkers, optical fiber sensor, CRP detection

44

## 45 **1 INTRODUCTION**

46 Inflammation is a non-specific response of the immune system to actual or potential infection  
47 [1] It is a defense mechanism necessary to maintain health because its purpose is to protect  
48 against the spread of injury and then restore the normal structural and functional state  
49 of damaged tissues [2]. Inflammation can be caused by various factors, i.e. contact with  
50 pathogens - bacteria and viruses - or non-infectious factors such as damaged cells, chemical  
51 irritants [3]. It triggers a chemical cascade of tens of molecules, which causes physical  
52 symptoms such as fever, high blood sugar, and pain. All of these chemical and physical  
53 symptoms are desirable unless they develop into chronic inflammation [4].

54 Two functionally related biomarkers are used to detect inflammation. One of them is the  
55 cytokine interleukin 6 (IL-6), which stimulates the production of the second important  
56 protein, which is the acute phase C-reactive protein (CRP)[5]. CRP protein has two varieties

57 [6]. The pro-inflammatory pCRP protein, which is secreted during inflammation. There is also  
58 the mCRP protein, which is involved in the restoration of damaged tissues even in the absence  
59 of inflammation [7,8]. Its role can be considered anti-inflammatory. In the literature, the vast  
60 majority of researchers analyse the pCRP protein as a factor of inflammation. It is a very good  
61 marker of the state of the body because its level changes very quickly when immunological  
62 dangers are detected. Up to a 1000-fold increase in CRP levels during infection is possible,  
63 and this increase occurs within a few hours [7]. Maximum production of CRP is achieved  
64 after 24-30 hours after inflammation offset [9]. The CRP level in a healthy adult human  
65 should not exceed 3 mg/L. The value above 5 mg/L is considered alarming, and above  
66 10 mg/L as a sign of inflammation [10]. The distinctions result from taking into account  
67 individual differences and the presence of inflammations with low CRP levels. If  
68 inflammation occurs, the type of infection can be determined from the CRP level [11–13]. If  
69 the CRP level does not exceed 40 mg/L, it is most likely a virus infection [14]. Bacterial  
70 infection increases the amount of CRP protein to a level above 60 mg/L [15,16] or 100 mg/L  
71 [17]. The CRP protein can also be used to assess the risk of cardiovascular events [18]. In this  
72 case, a level below <1 mg/L is a low risk, a level between 1 mg/L and 3 mg/L is a moderate  
73 risk, and a level above 3 mg/L is a sign of a high probability of a cardiovascular event [19].  
74 CRP is a very universal indicator, but still not fully comprehended. Much research is being  
75 done on its correlation with other diseases such as Alzheimer's [20], depression [19,21],  
76 various types of cancer [22,23], diabetes [24] and chronic dialysis [25]. Studies are also  
77 carried out to correlate the level of CRP in a specific disease with the appropriate treatment  
78 [26,27].

79 Usually, immunoturbidimetric and immunonephelometric tests are used for CRP  
80 measurements. The standard method is the high-sensitivity enzyme-linked immunosorbent  
81 assay (ELISA) [28]. Its sensitivity is on the level of pg/L [29] but is sensitive to the presence  
82 of non-specific proteins. ELISA is also a time-consuming method, requiring complex



83 detection steps and professional personnel [28]. CRP is a very important biological marker  
84 that is used in many aspects of the detection and treatment of inflammation and its genesis.  
85 For this reason, there is a need to create new sensors that will allow for accurate, easy, fast,  
86 safe, and highly sensitive measurement of the CRP level. In response to these needs, this  
87 article proposes a fiber optic sensor to detect the CRP level.

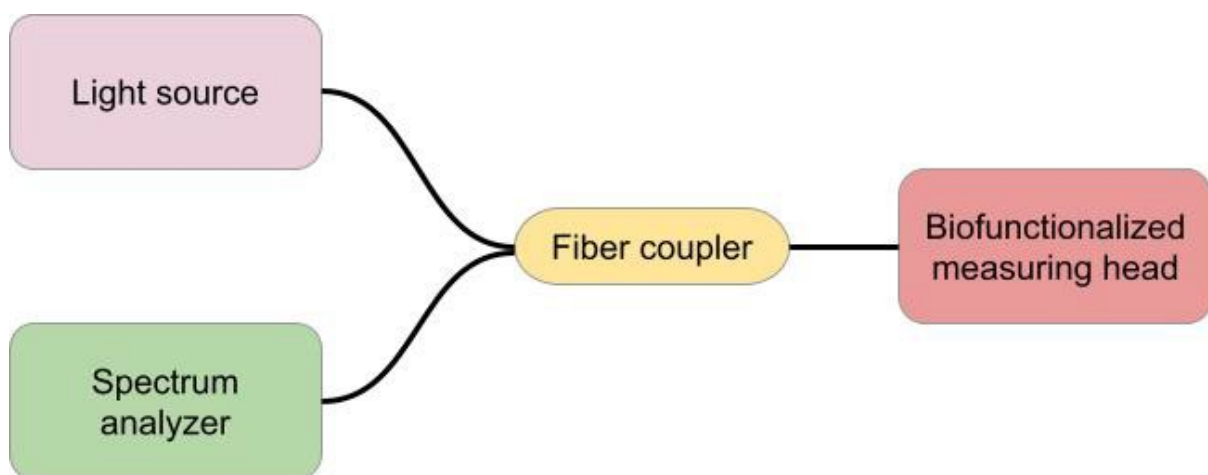
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## 89 **2 MATERIALS AND METHODS**

### 90 2.1 Measurement setup

91 The schema of the measuring system is shown in Figure 1. During measurements,  
92 a broadband light source emitting light with a central wavelength of 1310 nm (SLD-1310-18-  
93 W, FiberLabs Inc., Fujimi) was used. The light propagated through the fiber optic coupler  
94 (G657A, CELLCO, Kobylanka, Poland) into the biofunctionalized end-face of the optical  
95 fiber. Then, the wave reflected from the end-face of the fiber propagated to the detector,  
96 which was a spectrum analyzer (Ando AQ6319, Yokohama, Japan).

97



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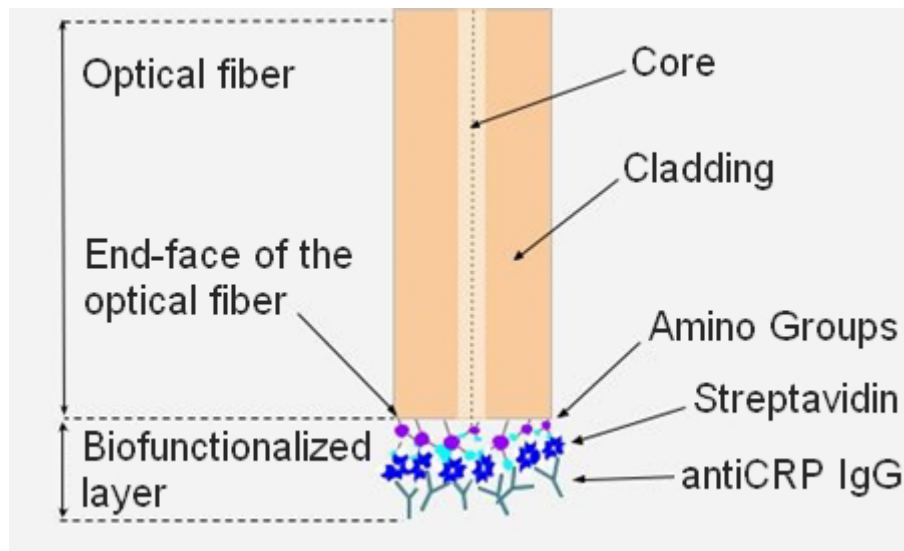
99 *Figure 1 Schema of the measuring system.*

100

### 101 2.2 Measuring head biofunctionalization

102 Optical fiber biofunctionalization was performed as follows. The molecular sieves (3 Å, Pol-  
103 Aura, Poland) were activated in an oven (10 hours, 350°C) and cooled, then transferred to the  
104 250 mL glass bottle with tight sealing and filled with dimethyl sulfoxide (molecular biology  
105 grade, Merck, Germany) or acetone (molecular biology grade, Merck, Germany) (1:1 (v/v)).  
106 Finally, left for 72 hours to dehydrate the solvents. The sensor was cleaned extensively by  
107 immersing it in H<sub>2</sub>O<sub>2</sub>/NaOH (WarChem, Poland; ACS reagent, Merck, Germany,  
108 respectively) water solution (10%, 25 mM respectively at 80°C) for 30 min. After the  
109 cleaning procedure, the optical fiber was immersed in ultrapure water and finally in  
110 anhydrous acetone solution to remove excess moisture (3 times in different solutions, each  
111 incubation lasted 10 min in an anhydrous environment). Cleaned optical fiber was immersed  
112 in a freshly prepared 1% 3- Aminopropyltriethoxysilane (99% purity, Merck, Germany)  
113 solution in anhydrous acetone for 12 hours in an anhydrous environment - to cover the optical  
114 fiber in amino groups. After 12 hours the optical fiber was immersed in anhydrous DMSO (3  
115 times, 5 min of incubation) to remove excess APTES solution. Cleaned optical fiber with  
116 amino groups on the surface was then immersed in a freshly prepared 10 mM stock solution  
117 of NHS-LC-Biotin (95% purity, Merck, Germany) in anhydrous DMSO and left for 24 hours  
118 in an anhydrous environment. Finally, after incubation, the sensor was immersed in the  
119 Streptavidin (1 mM solution, J&K Scientific, Poland) for 10 hours at 15 °C. Not immobilized  
120 protein was removed by washing in 1xPBS (Phosphate buffered saline tablets; Merck,  
121 Germany) solution. Finally, the sensor was immersed in biotinylated antiCRP IgG (1 µg/µL,  
122 Merck, Germany). After the antiCRP IgG attachment, a biological layer was formed at the  
123 end-face of the optical fiber, as shown in Figure 2.





124

125 *Figure 2 Elements of the biofunctionalized fiber head.*

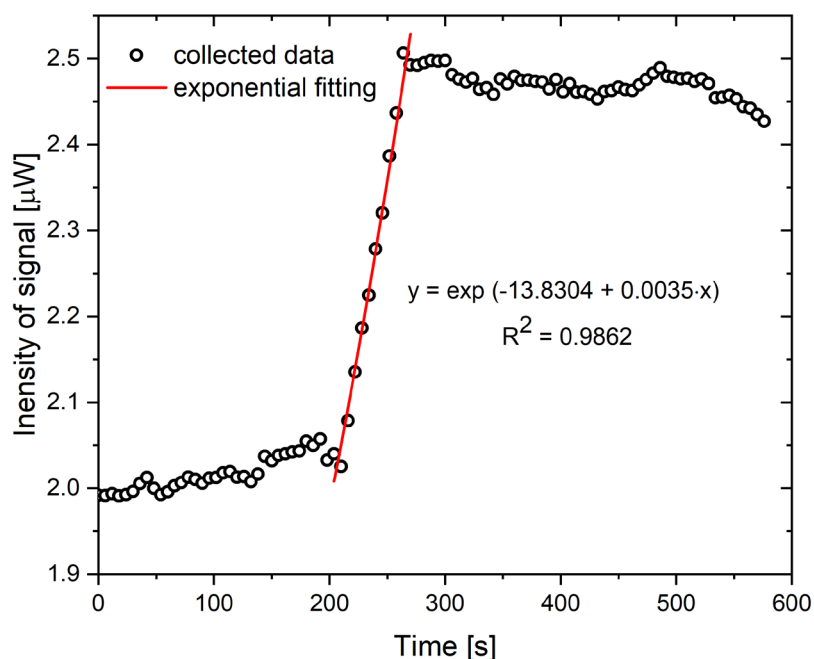
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### 127 3 RESULTS AND DISCUSSION

128 CRP detection consisted in carrying out a series of measurements of optical spectra during the  
 129 attachment of the protein to the antigens covering the measuring head. For this purpose, the  
 130 biofunctionalized measuring head was placed in a test tube filled with the solution. The tube  
 131 was filled with a solution of human CRP ( $1 \mu\text{g}/\mu\text{L}$ , Merck, Germany) in 1xPBS with  
 132 a concentration of  $5.65 \mu\text{g}/\text{L}$ . The occurring chemical interactions (hydrogen bonds, water  
 133 bridges) between the CRP protein and its antigens caused changes in the observed optical  
 134 signal. The test tube was held in a device that kept the temperature constant, which was  $25^\circ\text{C}$ .  
 135 After inserting the measuring head into the solution, the recording of optical spectra with the  
 136 analyzer was started. The optical spectra were recorded for 10 minutes, about every  
 137 6 seconds. To detect CRP, the change in signal intensity over time had to be observed. Data  
 138 analysis began with the analysis of a single optical spectrum. The received signal is noisy,  
 139 hence it was necessary to denoise it prior to its analysis. The FFT (Fast Fourier  
 140 Transformation) algorithm was used. FFT filtration consists in transforming the sampled  
 141 signal, i.e. a sequence of real numbers, into a sequence of complex numbers. In this way,  
 142 a frequency spectrum is obtained containing information about the signal components.  
 143 Unwanted components, e.g. those responsible for noise or not carrying important information,

144 are removed. The inverse transformation is performed and the result is a signal with selected  
145 components.

146 The next step in the signal analysis was to plot the changes in the intensity during the  
147 attachment of the CRP protein to the functionalized measuring head. The plotted curve, based  
148 on the studied changes in intensity, has exponential form between 200 and 250 seconds. The  
149 exponential characteristic of homopolyvalent antibody-antigen interaction is dependent upon:  
150 (I) – antigen concentration, (II) – surface immobilized antibody density and (III) – their  
151 orientation on the surface of the sensor head. Those characteristics regarding the interaction of  
152 pentameric CRP with immobilized antiCRP antibody was investigated by S.Lin et al. [30].  
153 Their results indicate the exponential characteristic of antigen/antibody interaction in different  
154 antigen concentration ranges and different binding stoichiometry forms (Ag1Ab1; Ag1Ab2,  
155 Ag2Ab1). To make it easier to observe, the resulting curve was averaged. The MAF (Moving  
156 Average Filter) algorithm was used, which calculates the mean value of a sample from a set of  
157 samples of the specified length. This length is referred to as the window. For the analysis of  
158 the measured signals, a rectangular window with a length of 8 samples was used. Time studies  
159 were carried out to investigate whether the CRP proteins had attached to the functionalized  
160 measuring head. They lasted 10 minutes and the result is shown in Figure 3.



161  
 162 *Figure 3 Change in signal intensity during antibody and CRP recombination. The plot presents collected data and the fitted*  
 163 *exponential curve .*

164 In the initial phase, which lasted about 200 seconds, the signal intensity value ranges from  
 165 1.98  $\mu\text{W}$  to 2.05  $\mu\text{W}$ . After this time, the rapid increase of the signal intensity appears due to  
 166 progressing sensor saturation. It reaches a value above 2.45  $\mu\text{W}$  and fluctuates around it. The  
 167 obtained characteristics are consistent with the theory. This means that the proposed sensor  
 168 enables the detection of CRP concentration of 5.65  $\mu\text{g/L}$ .

169  
 170 Detecting the CRP level is an extremely important element of diagnostics, which means that  
 171 research on dedicated sensors is extensive. Among others, the optical methods are  
 172 successfully used due to their unique properties. One of the solutions proposed in the  
 173 literature is the use of an optical cavity biosensor [31]. This system detects the local change in  
 174 refractive index caused by the adsorption of biomolecules on the receptor molecules. The  
 175 method is based on differential detection, which ensures high sensitivity. The system consists  
 176 of cheap parts and components as well as assures relatively simple operation. The test sample  
 177 is CRP standardized solution in an amount of 15  $\mu\text{L}$ . The entire measurement takes less than



178 30 minutes, the achieved limit of detection is 43.3 mg/L [31]. Another design of the optical  
179 sensor that can be used to determine the CRP level is a biosensor based on an long-period  
180 grating (LPG) made of double cladding fiber type W with graphene oxide [32]. The operating  
181 point was adjusted to the mode transition region by etching the fiber outer cladding, which  
182 increased the sensitivity while maintaining the visibility of the spectral features of the grating.  
183 The measurement time was 20/30 minutes and the detection limit achieved in serum was  
184 0.15  $\mu\text{g/L}$ . The clad etched fiber Bragg grating (FBG) sensors with graphene oxide were also  
185 developed [33]. The sensor has shown high sensitivity in the presence of interfering factors  
186 and wide linear range of operation. Detection limit was equal to 10  $\mu\text{g/L}$ , the measurement  
187 time lasted about 10 min, and the relatively high sample volume of 200  $\mu\text{g/L}$  was used. A  
188 different approach to create a sensor that determines the level of CRP utilizes a plastic optical  
189 fiber and a surface plasmon resonance (SPR) [34]. The sensor was integrated with a thermally  
190 stabilized microfluidic system. The detection was in human serum, and the lowest value  
191 detected was 9  $\mu\text{g/L}$ . The measurement lasted 15 minutes [34]. Another SPR-based fiber-optic  
192 biosensor working in a label-free manner was developed using dopamine as a cross-linking  
193 agent [35]. A multi-mode plastic clad fiber was used. The sensor shows satisfactory  
194 sensitivity and linear response. P. Zubiante et al. developed a fiber-optic sensor for detection of  
195 CRP utilizing Lossy Mode Resonance (LMR) [36]. The interaction of the protein with the  
196 aptamer results in the resonance wavelength shift. The constructed device achieved low limit  
197 of detection (62.5  $\mu\text{g/L}$  ), fast response time (61 s) and satisfactory sensitivity, as well as  
198 specificity. The measurement time was 700 s. The Table 1 shows a comparison of the solution  
199 proposed in this study with other selected methods described in the literature.

Number of method	Detection method	Sample	Sample volume	Detection limit	Measurement time	Ref
1	Proposed solution	CRP standardized solution	10 $\mu$ L	5.65 $\mu$ g/L	<10 min	N/A
2	Optical cavity sensor	CRP standardized solution	15 $\mu$ L	43.3 $\mu$ g/L	<30 min	[31]
3	LPG in double cladding fiber coated with graphene oxide	Human serum	40 $\mu$ L	0.15 $\mu$ g/L	20/30 min	[32]
4	clad etched FBG with graphene oxide	CRP standardized solution	200 $\mu$ L	10 $\mu$ g/L	10 min	[33]
5	SPR-based plastic optical fiber sensor	Human serum	20 $\mu$ L	9 $\mu$ g/L	15 min	[34]
6	SPR-based fiber-optic sensor	CRP standardized solution	no data	10 $\mu$ g/L	60 min	[35]
7	LMR-based fiber-optic sensor	CRP standardized solution	no data	62.5 $\mu$ g/L	11 min	[36]

201  
202 Among presented techniques, the sensor described in this study assures the smallest sample  
203 volume needed to perform a measurement. The requirement of the minimal sample usage is  
204 advisable as it is associated with a smaller amount of blood taken for testing. In terms of  
205 measuring time, the presented sensor is the fastest solution: achieving the measurement result  
206 is possible in less than 10 minutes. The achieved detection limit of 5.65  $\mu$ g/L is the second  
207 lowest result among presented methods, placing it behind a sensor with more complicated



208 manufacture procedure. A significant sample volume reduction, the shortest measurement  
209 time and relatively simple construction give a possibility of the wider use of the developed  
210 optical sensor outside the professional diagnosis laboratories. The obtained results of the  
211 preliminary studies performed in CRP standardized solution assure a strong basis for further  
212 research, involving measurements in real biological samples.

#### 213 **4 CONCLUSION**

214 Compared to other sensors for a CRP detection, the proposed sensor requires a small amount  
215 of sample (10  $\mu$ L), assures the shortest measurement time (<10 min), and its sensitivity is  
216 sufficient for medical measurements. The simplicity of its design and the possibility of  
217 constructing it from commercial elements are other advantages. As the sensitivity is  
218 acceptable for performing fast medical measurements, slightly worse measurement  
219 parameters compared to professional laboratory instruments requiring trained personnel to  
220 carry a long-time procedure are acceptable. Moreover, the proposed solution can be further  
221 miniaturized. The measurement head could be modified to a microsphere for additional real-  
222 time control of the sensors integrity in real-life applications [37]. The presented preliminary  
223 results are promising and constitute a strong base for further research, which will focus on  
224 establishing the full measuring range and determining sensor's parameters in real biological  
225 samples more precisely.

226

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237

## 238 AUTHOR CONTRIBUTIONS

239 Conceptualization, M.S.; methodology, M.S.; preparation of biofunctionalized fiber head,  
240 P.W.; measurements, P.W.; measurement data processing and analysis, M.K. and M.S.;  
241 writing—original draft preparation, P.W., M.K.; writing—review and editing, M.K, R.V. and  
242 M.S. All authors have read and agreed to the published version of the manuscript.

243

## 244 CONFLICT OF INTEREST

245 The authors declare no financial or commercial conflict of interest.

## 246 DATA AVAILABILITY STATEMENT

247 The data that support the findings of this study are available from the corresponding author  
248 upon reasonable request. Please, contact Małgorzata Szczerska at [malszcze@pg.edu.pl](mailto:malszcze@pg.edu.pl)

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