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

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5 Małgorzata Szczerska^{1,*}, Monika Kosowska², Roman Viter³, Paweł Wityk^{4,*}

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9 ¹ Department of Metrology and Optoelectronics, Faculty of Electronics, Telecommunications
10 and Informatics, Gdansk University of Technology, 11/12 Narutowicza Street, 80-233
11 Gdansk, Poland

12 ² Faculty of Telecommunications, Computer Science and Electrical Engineering, Bydgoszcz
13 University of Science and Technology, Al. Prof. S. Kaliskiego 7, 85-796 Bydgoszcz, Poland

14 ³ Institute of Atomic Physics and Spectroscopy, University of Latvia, 19 Raina Blvd., Riga
15 LV-1586, Latvia

16 ⁴ Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk,
17 Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland

18

19 *Correspondence

20 Małgorzata Szczerska, Department of Metrology and Optoelectronics, Faculty of Electronics,
21 Telecommunications and Informatics, Gdansk University of Technology, 11/12 Narutowicza
22 Street, 80-233 Gdansk, Poland

23 Email: malszcze@pg.edu.pl

24

25 Paweł Wityk, Department of Biopharmaceutics and Pharmacodynamics, Medical University
26 of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland

27 Email: pawel.wityk@pg.edu.pl

28

29

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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.

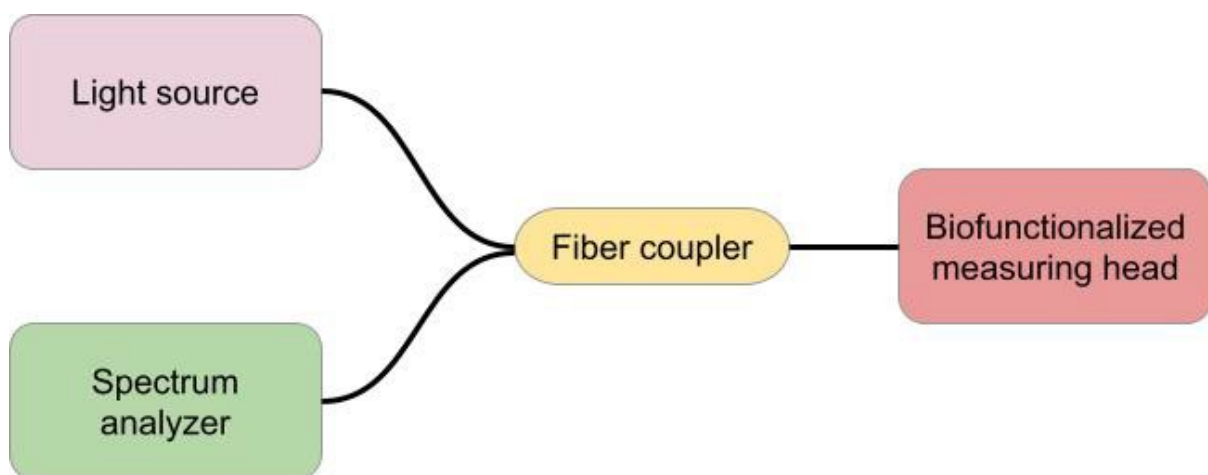
88

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).

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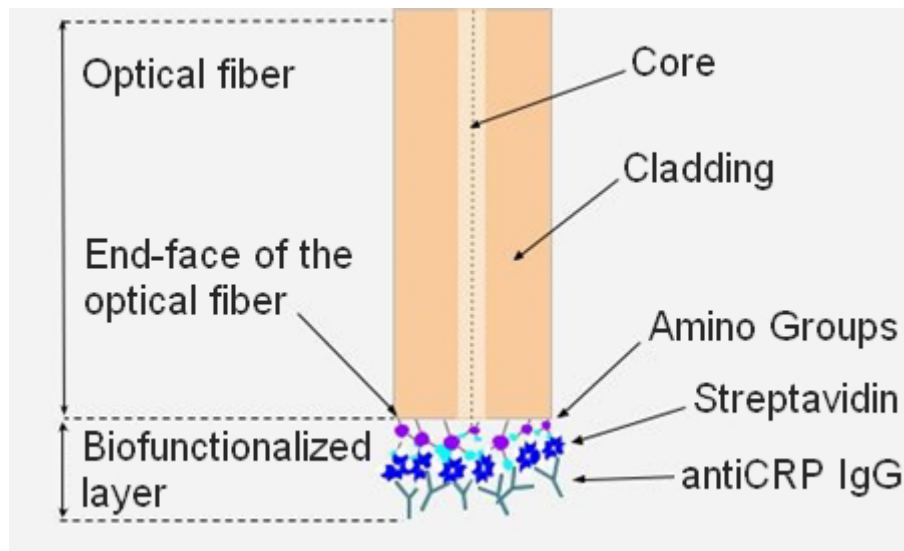
99 *Figure 1 Schema of the measuring system.*

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 H₂O₂/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.*

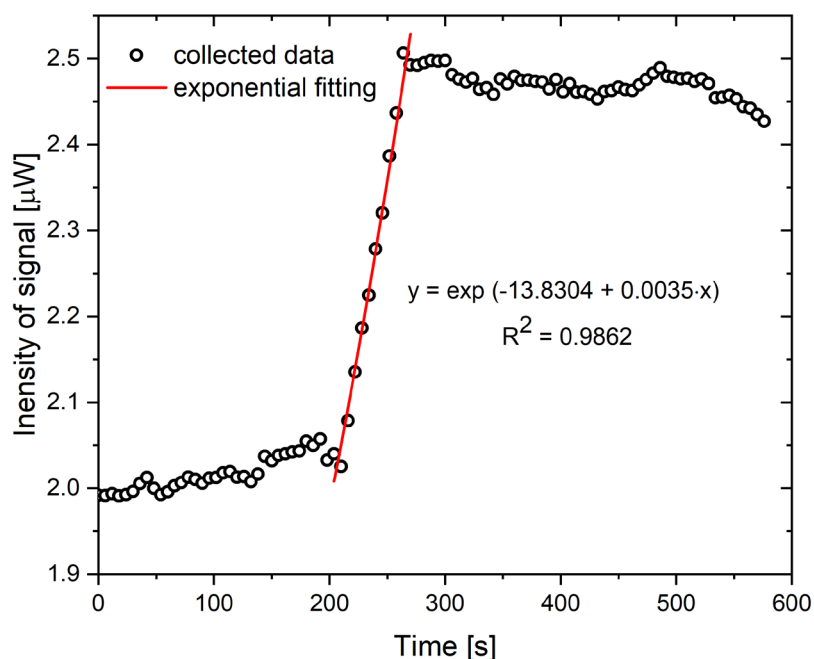
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127 3 RESULTS AND DISCUSSION

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°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 μW to 2.05 μW . After this time, the rapid increase of the signal intensity appears due to
 166 progressing sensor saturation. It reaches a value above 2.45 μW 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 μL . 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. Zubiarte 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 μ L	5.65 μ g/L	<10 min	N/A
2	Optical cavity sensor	CRP standardized solution	15 μ L	43.3 μ g/L	<30 min	[31]
3	LPG in double cladding fiber coated with graphene oxide	Human serum	40 μ L	0.15 μ g/L	20/30 min	[32]
4	clad etched FBG with graphene oxide	CRP standardized solution	200 μ L	10 μ g/L	10 min	[33]
5	SPR-based plastic optical fiber sensor	Human serum	20 μ L	9 μ g/L	15 min	[34]
6	SPR-based fiber-optic sensor	CRP standardized solution	no data	10 μ g/L	60 min	[35]
7	LMR-based fiber-optic sensor	CRP standardized solution	no data	62.5 μ 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 μ 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 μ 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

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