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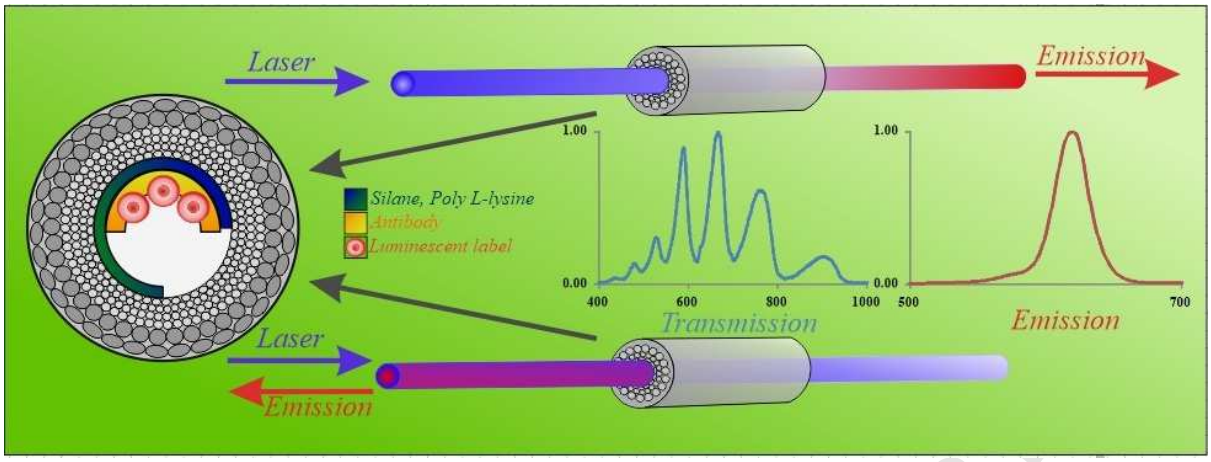

Microstructed Optical Fibers Based Luminescent Biosensing:

Is There Any Light at the end of the Tunnel? - A Review

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Abstract:

The review covers the current state of the art of luminescent biosensors based on various types of microstructed optical fibers so called microstructed optical waveguides (MSWs). The unique optical and constructive properties of MSWs that make it possible to consider them one of the most promising integrated platforms for bioassay are described. Separate sections are devoted to a) MSWs classification, b) MSWs materials, c) aspects of biosensing, based on biomolecules incorporated into MSWs, d) development of models for prediction of effectivity of luminescent signal processing. The authors' view on current trends and limitations of MSWs for biosensing and the most promising areas and technologies for application in analytical practice is presented.

Keywords: microstructed optical fiber, photonic crystal fiber, biosensor, luminescence, optical sensing.

Abbreviations: MOF, microstructed optical fiber; MSW, microstructed waveguide; PC, photonic crystal; PCF, photonic crystal fiber; PBF, photonic bandgap fiber; LPG, long period gratings; QD, quantum dots; SCW, solid core waveguide; HCW, hollow core waveguide; SC MSW, microstructed waveguide with suspended core; HC PCF, hollow core photonic crystal fiber; HC LPG, microstructed hollow core LPG waveguides; PC6, enzyme proprotein convertase 5/6; ERα, estrogen receptor; CRP, C-reactive protein; MB, molecular beacons; LAPAP, laser-assisted protein adsorption by photobleaching.

1. Introduction

Bioassay is one of modern trends in analytical chemistry. In this field of knowledge the most tempting is the development of multifunctional platforms, which integrate the functions of solid support and signal transducer. Sensor systems based on optical fibers are the promising tool in this field. They combine the advantages of miniaturization, long interaction length, small sample volume and possibility of integration to various sensor systems [1]. In terms of improving the analytical characteristics, systems with possibilities of selection and reorganization of the target optical analytical signal are especially important in the development of technologies for life sciences research, biosafety, biomedical diagnosis, tissue pathology and blood flow monitoring. Microstructed optical fibers (MOFs) so called microstructed waveguides (MSWs), which are 2D photonic crystals (PCs), occupy a special place among optical fibers.

They are characterized by a presence of a solid or hollow core, which acts as a waveguide defect, surrounded by a structural cladding significantly affecting on the transmission of the optical signal.

A number of recent reviews focus on the use of MSWs in the development of various sensory systems, including biosensors [2-7]. Application of photonic crystals in the development of modern methods of bioassay is discussed in [2, 8]. The review [8] examined and summarized results of the development and application of materials based on PCs: PC films, microcarriers, fibers and optofluidic devices to enhance both fluorescence and label-free analysis. The use of photonic crystal fibers (PCFs) as the sensor platform and high-performance micro-reactor for chemical sensing and photochemistry is discussed in [9]. High efficiency of PCFs for photoactivation, sensing of biological objects and their ability to study the photochemical and catalytic reactions is demonstrated. Features and characteristics of the MSWs in UV, visible and IR spectral regions for biomedical research and clinical practice are discussed in [10]. Modern trends in the development of sensors based on PCFs are discussed in [11]. The different platforms that can be applied for PCF sensors development, such as Bragg gratings, long period gratings (LPG) and PCF interferometers are compared.

The analysis of these works allows us to highlight certain advantages and disadvantages of biosensors based on MSWs using various methods (Table 1).

Table 1

Luminescence spectroscopy is one of the most selective and sensitive optical analytical methods. In our opinion, in spite of a number of works devoted to the study of the luminescence properties of organic dyes and quantum dots (QDs) in MSWs and developing MSW based luminescent sensors, a paradoxical situation has emerged in this field. On the one hand, the ultra-high sensitivity of MSWs based sensory systems, including luminescent, is well demonstrated, but at the same time these systems are not put into practice. For instance, the authors [12] discuss in detail fluorescence based fiber optic and planar waveguide biosensors, however MSWs based bioluminescent systems are not specifically addressed. The main reasons for this are the insufficient awareness of the analytical community of potential of MSW based sensors, the limited commercial availability of such fibers [13, 14], as well as the lack of simple and cheap devices for analytic signals detection. The luminescence detection in MSWs can be performed with optic scheme including in general case: broadband and/or narrowband light source, fiber fixing device, lenses and spectrum analyzer. In the case of flow assay, fiber couplers are used as adaptors for liquid flow through MSWs. Some examples of set ups are presented in the section “Microstructed optical fiber based luminescent bioassay”.

Here we present the practical view on analytical application of MSWs for the analysis of biological molecules using luminescence spectroscopy at the present and future. The overview can simplify the selection of the necessary components for specific applications in analysis.

2. Types of microstructed waveguides

At present there is no clearly accepted classification of microstructed fibers therefore we based on Russell's classification [9] and extended it to others MSWs. The main classes of structured waveguides are (*i*) solid core waveguides (SCWs) and (*ii*) hollow core waveguides (HCWs).

Solid core waveguides

The following subclasses of SCWs can be distinguished: microstructed solid core LPG waveguides, microstructed waveguides with suspended core (SC MSWs), nonlinear photonic crystal fibers with solid core, large mode area photonic crystal fibers with solid core, Kagome photonic crystal fibers with solid core [15] (Fig. 1). The total internal reflection is the main light propagation mechanism in this class waveguides [16]. It should be noted that SCWs with photonic bandgap guidance are recently investigated [17].

Figure 1

Some of the remarkable properties of SCWs defining their applicability in analytical practice are endlessly single-mode behavior [16, 19], high birefringence [20], large mode area [21] and efficient dispersion management, including ultra-flattened [22] and strongly anomalous dispersion [23]. These SCWs properties allow to improve precision of target analytical signal. The long length of light interaction with analyte is of particular importance in terms of the MSWs application in analytical practice for increasing sensitivity. SCWs could be

applicable as solid support for heterogeneous assay formats, where reagents are immobilized on the SCW central defect surface.

Hollow core waveguides

The following subclasses of HCWs can be distinguished: hollow core microstructed waveguides, photonic crystal fibers with hollow core (HC PCFs), Kagome with hollow core, Bragg waveguides with hollow core, microstructed hollow core LPG waveguides (HC LPG) (Fig. 2).

Figure 2

Several light propagation mechanisms can be performed in HCWs. Constructive interference of scattered light (or light propagation under the influence of photonic forbidden bands) is observed in case of lattice constant less than the optical wavelength. The Fabry-Perot etalon reflection spectrum is formed for waveguides with lattice constant larger than the optical wavelength. In [24-26] HC LPGs are considered as the system with embedded Fabry-Perot resonator which is formed by the capillary walls of structure cladding. Light with a resonance wavelength penetrates into the cladding, leaving a hollow structural defect, and the corresponding light mode in the waveguide rapidly damps. Hollow core microstructed waveguides with anti-resonant light propagation are perspective for analytical applications.

HC LPGs are characterized by a large hollow core diameter – more than 100 μm, and proportionally big diameter of capillaries in cladding [27]. Microphotograph of

the cross section of HC LPGs (chirped HCWs) and its transmission spectrum are presented on the Fig. 3. Shown spectral characteristics acquired for HC LPGs with wide capillary walls (2.5μm) and large (280 μm) hollow core prove the assumption that internal glass walls representing a build-in Fabry-Perot interferometer.

Figure 3

And finally the third way of light propagation mechanisms is Bragg's reflection from periodic array of cladding [16, 28] and antiresonant reflecting from the first high-index layer [26]. Bragg PCFs can provide unique dispersion [29] and nonlinear characteristics that have been used to demonstrate a number of new effects, including the generation of a broadband supercontinuum and a zero group-velocity dispersion [30-32].

It should be noted that whereas for SCWs the interaction of light with analyte takes place exclusively on the surface of the central fibers defect, then for HCWs the process passes in the hollow defect volume [9], which significantly increases the interaction degree. HCWs could be applicable as solid support for heterogeneous assay formats, (immobilization of reagents on hollow core inner surface) and microcontainer (all reagents are dissolved inside the hollow core).

It should be noted that the classification of MSWs given above is by no means complete or fully worked. Continuing emergence of varied MSWs architecture and their application in original analytical schemes [33-40] suggests we shall see the great progress in developing of MSWs based sensor elements in the near future.

3. Materials for microstructed waveguides manufacturing

Currently, a range of different materials can be used to make MSWs. A lot of reports of MSWs have described fibers made of silica [41, 42], of different types of glass (soft glass [27, 43, 44], fluoride and chalcogenide glasses [45-48], tellurite glass [49, 50], flint glass [51]) and of polymer [52, 53].

Silica is the dominating material due to its optical and mechanical properties, such as good transparency in UV, visible and NIR spectral ranges, high mechanical strength against pulling and bending [41, 42]. Different types of soft glass may be suitable for making MSWs, since they have similar to silica optical properties, but much lower melting point, which is near 600°C and such glasses are, commonly, cheaper [27]. The MSWs made from fluoride and chalcogenide glasses have low transmission losses and can be used for generation of supercontinuum, i.e. generation of coherent optical radiation with ultra broad spectrum (few optical octaves). The major disadvantages of fluoride and chalcogenide glasses are high cost and high brittleness. It is necessary to single out so-called hybrid MSWs, in which chalcogenide is deposited on the inner walls of the MSW holes [54].

Polymer fibers provide high numerical aperture, and its chief advantage is robustness under bending and stretching, so these fibers are well suited for data transmission [55]. The first fluorescence-based poly(methyl methacrylate) MSWs biosensor was discussed in [56]. Polycarbonate polymer MSWs [57] and in particular humidity insensitive TOPAS [58] and Zeonex [59] MSWs can be

prospect in biosensing because they will not swell and change properties when being in liquids such as blood and water.

4. Microstructed optical fibers based luminescent bioassay

MSWs were used as a base for DNA, immuno- and enzymatic assays with luminescent evaluation of outcomes. Two main formats of luminescent assays are commonly used in sensors: (*i*) Heterogeneous, where one reagent (single stranded oligonucleotide, antibody, antigen or enzyme) is bound to a solid surface. In the case of reagent attachment to MSWs surface, the fiber plays the role of both a solid support and a signal transducer; (*ii*) Homogeneous, where all reagents are distributed in solution, providing fast kinetic of one-phase reaction. Since the interaction of reagents occurs in solution, a luminescent signal appears in the volume of solution filled hole(s).

The enzymatic, immunochemical methods and DNA analysis dedicated to luminescent analysis of biomolecules in MSWs are summarized in Table 2.

Table 2

4.1. DNA detection

The DNA detection is important in medicine, pharmacy, forensics and archaeology. It is therefore not surprising that optical fibers, including MSWs have been employed for this purpose. The current state and prospects of application various types of optical fibers biosensors, including luminescence based, for DNA

analysis are discussed in detail in [60]. The article focuses on DNA assay by evaluating the effect of different DNA sequences on the modification of the properties of optical fibers and comparison of different formats of analysis and immobilization. The authors consider the prospects of MSWs for DNA optical fiber sensors development. There are several examples of label-free DNA sensors based on localized variations in the refractive index of MSWs coating with DNA layer upon hybridization with complementary DNA sequences [61]. Drawbacks of DNA label-free sensing are possibility of non-specific binding and problems with detection of multiple DNA targets. Therefore, labeled DNA detection based on fluorescence label is still the preferred approach to DNA sensing. The first to demonstrate the implementation of MSW biosensors into small biochips for controlled fluid and light handling were Rindorf et al [62].

Sensor for specific DNA sequences based on molecular beacons (MB) immobilized on the internal surfaces of suspended core silica glass optical fibers was demonstrated by [63]. MB is single-stranded oligonucleotide hybridization probes with covalently linked fluorophore and quencher. The fluorophore's emission is restored when MB bind to a target nucleic acid sequence. Therefore the MB applying does not require the labeling of complementary DNA sequences before detection. The high cost and complicated synthesis of MB prevent their wide application for practical purposes. In this aspect, the low-volume MSW sensing capability is a critical for using of MB probe and MSWs with possibility of combination of low sample and reagents volume with long optical way. The

geometry of SC MSWs and the schematic diagram of the final surface state of the MB functionalized fibers are presented at the Fig. 4.

Figure 4

Combination of the layer-by-layer technique and the biotin-streptavidin binding was performed for linking of biotinylated MB on the surface of the SC MSWs. The hybridization test was carrying out between the SC MSWs immobilized with MB and the complementary, non-complementary sequences DNA and oligonucleotides differing by a single base. The enhancement of luminescence was observed in a case of solution contained complementary sequences DNA. It is interesting to mention, luminescence was enhanced for 30% (comparing with non-complementary DNA) in a case of oligonucleotides sequences differing from the target by just one base. Thus, the data [63] demonstrated that the functionalized SC MSWs can serve as a base for highly specific DNA sensor.

The interesting approach - laser-assisted protein adsorption by photobleaching (LAPAP) was presented in [64]. This method involves a facile photo-immobilization of biomolecules (fluorophore-conjugated) on albumin-passivated substrates resulting in the photobleaching of fluorophore. The protocol of LAPAP included two steps: (i) passivation of pure silica PCFs air holes with a base layer of bovine serum albumin and (ii) photo-immobilization of biotin-4-fluorescein via excitation 490 nm. The formed bioactive surface was qualified with dye-conjugated streptavidin-Atto488 (Atto488Strep). Atto488's absorption (500 nm)

and emission (523 nm) peaks were observed and indicated of the presence of biotin-bound Atto488Strep, implying a successful photo-immobilization of biotin-4-fluorescein. Fiber-coupled LED (2.3 mW, Thorlabs M490F1) was employed as for photo-immobilization as well as for luminescence detection of Atto488 (Fig. 5). According to authors [64] the main advantage of LAPAP comparing with covalent or electrostatic layer-by-layer coating is an absence of any surface pre-activation procedures.

Figure 5

The high reproducibility of measurements after two hybridization steps in DNA assay and possibility of re-using of the same fiber for several detections was demonstrated by [60].

The introduction of polymerase chain reaction (PCR) into a wide practice allowed to increase the sensitivity of DNA assay in comparison with the microscopy of native and labelled samples by more than 1000 times. The combination of PCR with the use of MSWs based biosensors, which are the theoretically ideal collector and transducer of the optical signal and can detect the luminescence at picomolar level, allows to hope for the soon developing of DNA detection techniques with significantly lower detection limits due to additional enhancement of luminescence signal in MSW site than currently being used methods. It is worth mentioning a much smaller required volume of the sample and a possible reduction in the sample preparation time in this case.

4.2. Immunochemical analysis

Conventional approach for heterogeneous immunochemical analysis in MSWs is the pretreatment of its inner surface for immunoreagents binding. Some features of this pretreatment, including those related to the possibility of estimating the amount of silanol groups at HC PCF surface were recently described in [65].The deposit of surface layers within the fiber holes is the best way for biofunctionalization of the MSWs. Poly-L-lysine and nm-scale silane layers were successfully used for silica and glass LPG PCF modification [66, 67].

Monro et al. [68] has investigated the applicability of this technique for antibodies immobilization inside soft glass microstructed fibers. This approach combines the sensitivity based on the long interaction lengths with the selectivity occurs by the use of highly specific antibodies. The soft F2 glass SC MSWs used in work [68] had a fiber core that was suspended in air by 3 long fine struts within a robust jacket (Fig. 6). The SC MSWs were functionalized from the fiber ends and technique for depositing coatings on the internal surfaces of the holes within the cross-section and along the length of the fiber was developed. The antibody immobilization procedure included (*i*) the silanization of surface with 3-mercaptopropyltrimethoxysilane; (*ii*) the attaching of cross-linking layer (N-γ-maleimidobutyryloxy succinimide ester) and (*iii*) the attaching of antibodies to the crosslinker. To determine whether the antibodies were attached to the glass, they were labeled with QDs (Qdot800) and the luminescence intensity measurements of Qdot800 were made at the opposite end of the fiber from which the pump light is

launched. The strong QDs luminescence indicated that the labeled antibodies have become attached to the core surface.

Figure 6

It should be noted that the choice of QDs as biolabels must also take into account the spectral features of used MSWs. Red shift of QDs luminescence in HC PCFs was described in [69].

A method for estrogen receptor (ERα) protein detection in commercially available silica F-AIR-6-800 HC PCF [70] using specific luminescent-labeled antibody was described by [71]. The determination of breast carcinoma cell lysates direct immobilized inside HC PCF was carried out using anti-ER primary antibody and goat anti-rabbit IgG labeled with green (Alexa™ Fluor 488) and red (Alexa™ Fluor 555) fluorescent dyes as the secondary antibody. Protein immobilization on fiber inner surface was performed by the pre-activation of surface with poly-L-lysine (0.01%). The immobilization protocol included subsequent binding of target protein (positive MCF-7 or negative MDA-MB-231 breast carcinoma cell lysates), anti-target protein antibody (primary rabbit antibody raised against ER protein) and secondary antibody with fluorescent tags. The schematic setup used for the spectral analysis of luminescent proteins is shown in Fig. 7. Lasers with two wavelengths (473 and 532 nm) were used for the excitation. The protein binding inside the fiber was detected with fluorescence microscopy and confirmed by spectroscopic analysis. The control fibers showed no emission peaks, whereas green and red dyes

emission was observed in MCF-7 contained fibers. Luminescent signals of both dyes were found to increase linearly to the concentration of cell lysate. The described methodology demonstrates high sensitivity and can detect 20 pg of ER protein in 50 nL sample volume.

Figure 7

Highly efficient biosensing based on detection of luminescent labeled biomolecules signal was suggested in [72]. The scheme of set up is presented in Fig. 8.

Figure 8

Small solid core low index soft glass SC MSWs (lead silicate glasses SF57, F2 or LLF1) performed as the triangular central core optically isolated from the outer solid glass region via three fine supporting struts was used in this work [72]. The luminescence of CdTe/ZnS QDs labeled goat $F(ab')_2$ anti-mouse antibody within SC MSWs was detected using near infrared light at labeled antibody concentration as low as 1 nM via direct measurements from the output end of the fiber. Extremely small sample volume (of order 10 pL) was used. According to the authors, the results obtained are limited exclusively by the intrinsic glass luminescence and the formation of crystals from the buffer solution components.

Most of MSW biosensors described are designed to detect single type antibodies, In [73, 74] authors present the selective measurement of two different antibodies inside a polymer SC MSWs. MSWs were fabricated from chemically inert polymer

(cyclic olefin copolymers, TOPAS) and photolinker anthraquinone was attached to the surface and activated by UV light. Multianalysis was carried out on different sites of sensor layer inside a single fiber. For this purpose antigens (streptavidin and C-reactive protein, CRP) were immobilized on different ends of the SC MSWs and specific to streptavidin and CRP labeled antibodies were detected. Standard fluorophore marker molecules Cy3 (λ_{abs} =550 nm, λ_{em}= 570 nm) and Cy5 (λ_{abs} =649 nm, λ_{em}= 670 nm) were used for labeling of antibodies against streptavidin and CRP, respectively. The luminescence was detected on the output end of the fiber and "cross-talk" between the two sensor sections was observed.

4.3. Enzyme based analysis

Although enzymatic reactions are extensively used to develop fluorescence based fiber optic and planar waveguides biosensors [75], there is only single example of enzyme analysis in MSWs [76]. A luminescence-based homogeneous assay of enzyme proprotein convertase 5/6 (PC6), as important potential biomarker of endometrial receptivity, caused by its cleaving activity, has been demonstrated within a small-core SC MSWs [76]. The fibers architecture is shown in Fig. 6. The analyzed solution was placed into silica MSWs without any core surface pretreatment. PC6 concentration was detected in model solution at level down to 50 U/mL by appearance of luminescence after release of quenched 7-amino-4-methylcoumarin from a peptide substrate, which then becomes fluorescent. Enzyme activity was measuring as the rate of increasing of luminescence intensity.

Low sample volume (210 nL) and, potentially, *in vivo* application as the main advantages of the supposed platform has been shown.

In the work [65] authors presented detailed scheme of enzyme horseradish peroxidase covalent binding to functionalized with (3-aminopropyl) triethoxysilane hollow core surface of PCF and demonstrated the possibility for biosensor element creation.

Nevertheless, no more enzyme-based MSW sensors were reported. Potential restrictions for this approach could be related with distortions, associated with the accumulation of products of an enzymatic reaction in a small MSW volume.

As an outcome for luminescent labeling it is necessary to mention, that the high density of the light field in MSWs makes it difficult to use luminescent dyes (even modern with high photostability) as labels because of their high sensitivity to photobleaching [77]. Opposite, luminescent nanoparticles, first of all semiconductor QDs, which are extremely stable for photobleaching and emit narrow emission bands, could be a promising alternative [78-80]. It is very important to mention the appearance of modern synthesis conception of QDs with high quantum yield [81] and new detection strategies [82, 83]. Moreover other new luminescent inorganic nanomaterials, especially metal nanoclusters, become to be more and more popular because of some advantageous properties and are currently recommended for bioanalysis because of their biocompatibility and optical stability [84-87].

5. Luminescent signal optimization

Development of models linking the MSWs geometric structure with the properties of resulting luminescent signal is an important task in creating of sensor devices based on MSWs. At the same time it is important to develop approaches for the optimization of MSF-based biosensors in the terms of luminescent signal detecting technique.

For the best of our knowledge, the first to consider the problem were Konorov and Zheltikov in [88]. They compared two PCF sensors. In the first sensor, laser radiation was delivered to a sample through the central core of dual-cladding PCFs with a diameter of a few micrometers, while the larger diameter cladding was used for collection and guiding of the luminescent signal to a detector in the backward direction. In the second sensor, liquid sample was collected by the PCF claddings and interrogated by laser radiation guided in PCF modes. Cross-referencing measurements thus demonstrated the equivalence of spectroscopic data from these two PCFs and the data obtained in standard cell. It was established that for liquid samples with refractive indexes exceeding the refractive index of PCF material, PCFs can guide laser light by total internal reflection, providing an 80% overlap of interrogating radiation with fluid.

The first attempt to establish a common model of joint excitation and emission within the fluid-filled SCWs was made by Monro et al [89-91]. An expression for the efficiency of luminescence capture fraction for an arbitrary MSWs based on vectorial solutions of Maxwell’s equations was developed [89]. The effective radius was found by the assuming that the holes of the MSWs are circular with the

same area as that of the real fiber. The discrepancy between the theoretical and experimental results was explained due to accordance with the severity and carelessness of this assumption. Theoretically predicted improvement of capture luminescence fraction up to 2 orders of magnitude for the MSWs from the glass with high refraction index was established. It has been experimentally confirmed that this effect results in localized, high intense electromagnetic field at the interface of the glass and holes, making them an ideal for thin layer sensing of the analytical signal. It was shown that the normalizing fraction of input power to the capture of the luminescence excitation compensates the signal loss, due to the small diameter of the holes, by increasing power of the excitation signal in the fiber and the use of buffer fibers with high numerical aperture.

The authors made an attempt to extend the proposed model taking into account the effect of not only forward propagating modes (Φ_f), but the luminescence radiation propagating in the backward modes ($\Phi_в$) relative to the excitation source [90]. The theoretically calculated and experimentally tested parameters $\Phi_в$ and Φ_f were compared. On the basis of the calculated and experimental data it was found that the radiation propagating in the backward modes is more powerful and thus more suitable for analytical signals registration [90]. $\Phi_в$ registration is characterized by the follow possibilities: implementing real time measurement, dip-sensing configuration, higher signal to pump ratio, easiness of use in terms of keeping the launching end of the setup intact and using the exit end for filling. The dependence of the luminescence intensity of the detected signal for $\Phi_в$ and Φ_f from fiber

lengths was calculated. The authors demonstrated the possibility of a significant increase in Φ_e due to the formation of high-intensity regions in the case of an optimal geometric configuration of the fibers, despite the relatively low power level in the holes. Established results in [91] show SC MSW fluorescence sensors can be up to 55 more efficient in comparison to conventional fiber tip sensors.

Selective filling of MSWs with the collapsed (closed) cores and separation out excitation and collection signal was discussed in [92-95]. The launching in to only one core of the fiber and using a second core for collection of the fluorescent light was investigated by [92]. Due to focusing of luminescence generation within the holes inside the fiber it is more efficiently captured in to the second core than glass fluorescence, which overlaps more strongly with the first core, what results in an improvement in the signal fluorescence to background fluorescence ratio.

To resume this paragraph it is important to mention that currently developed mathematical methods are in relatively good agreement with the experimental results. Their further development in conjunction with the improvement of experimental techniques will allow for full use of the MSWs sensor advantages.

Conclusion and outlook

Among the main advantages of MSWs as a promising biosensing analytical platforms it is necessary to note: the nature of MSWs as a highly efficient microreactor, rather simple surface modification protocols and the possibility of relatively simple integration into perspective analytical devices for creating a

complex optical path configuration with practically zero dispersion of the signal. It is important to mention the substantial stability of MSWs to the fluctuations in the spectral structure of the light source due to single-mode behavior of the light inside the fiber allowing using not only single-mode, but multimode sources with coherent light. This phenomenon also significantly reduces the effects of irregularities in incoherent sources emission spectrum and makes it possible to use low cost LED in sensor system. The management of location forbidden photon energy bands in transmission spectra by designing of MSW architecture allows to significantly reduce non-target signals by cutting out some spectrum ranges.

Application of luminescence as analytical signal, especially QDs luminescence which is characterized with high intensity and narrow emission bands, in combination with the above-described properties of the MSWs [96, 97] and their opportunity to act as a theoretically absolute analytical signal collector allow to move from mainly described so-called "luminescence MSW sensors" which are in fact detectors to Wolfbeis's definition of real biosensor as "miniaturized analytical devices that can deliver real-time and on-line information on the presence of specific compounds or ions in complex samples" [1].

However, the development of real MSW sensors for bioassay is currently in the infant state. This is due to a number of reasons, including the relatively high current cost of MSWs in comparison with conventional fibers, a fairly limited range of manufacturers, the difficulty of accurate modeling of complex systems based on the MSWs. However, in order to create and implement real MSWs

luminescent based biosensors in the analytical practice, it is necessary to determine a certain road map and solve the following issues:

1. MSW-based luminescent biosensors are by no means a panacea. It is necessary to define more precisely the range of tasks for which the application of these systems can yield breakthrough results. It is clear, such complex systems would not be relevant for the routine assay of regular analytes. They will be very relevant in a relatively narrow field of application, where high sensitivity, low sample volume and the use of expensive or rare reagents are required. In our opinion, such tasks, for example, may include the rapid determination of picomolar concentrations in the diagnosis and treatment of cancer tumors, and analysis of toxicants such as dioxins. The use of MSW based sensors in these cases can be justified not only by high sensitivity, but also by the possibility of minimizing the sample preparation time.

2. SCWs and HCWs with different types of architecture, especially SC MSWs, LPGs and HC PCFs, can be the most promising platforms for the creation of luminescent based biosensors. These structures combine direct and, as a result, the most effective interaction of light with a sample on the surface of a suspended or in the volume of a hollow central defect, microliter sample volumes and the possibility of a significant increase in pump power. The use of such structures in combination with QDs based labels allows us to hope for an increase in the sensitivity of the sensors to the level of picomolar concentrations.

3. It is extremely important to continue improving the MSWs production technologies, their subsequent processing, creating simple and low cost luminescence signal readers.

The combination of these properties and approaches allows us to look optimistically into the future and hope that in the coming years we will see the light at the end of the tunnel of creating effective and commercially available fluorescence MSFs based biosensors.

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Table 1

Advantages and disadvantages of main approaches to the development of biosensors based on microstructed waveguides

Advantages	Disadvantages
Label free analysis on Bragg and long period gratings	
Possibility to measure strain, temperature, curvature, pressure on the base of changes in the location and characteristics of photonic band gaps.	High sensitivity to strain, temperature, curvature, pressure may decrease the results reproducibility.
Simple interferometric devices.	Operation mostly in transmission mode and broad resonance peaks (for long period gratings) leads to low specificity.
The comparative cheapness and easiness of fabrication and detection.	
High sensitivity to refractive index changes.	
Molecular absorption based on surface plasmon resonance	
High sensitivity to changes in the refractive index of the dielectric medium.	Coating the MSW holes with metal film is difficult and time-consuming.
Low optical loss of the Gaussian guided mode.	
Refractive-index resolution for aqueous analytes is 10^{-4} RIU.	Control of polarization state of the optical wave propagating in the fiber is required.
Easy achieving of phase matching between the core mode and the plasmon.	

Advantages	Disadvantages
Surface-enhanced Raman scattering	
Possibility of label-free detection because almost every compound (in particular organic compounds) has its own Raman spectrum. Insensitiveness to the presence of oxygen. Possibility of multicomponent analysis due to narrow Raman peaks. For gas analysis possibility to use continuous flow detection and ability to multiple- time application.	Low Raman cross-section leads to poor sensitivity with LOD above 10^{-3} M for Raman spectroscopy and ~10^{-6}–10^{-7} M for SERS. Requirement of sorption and strong attachment of target molecules to the SERS substrate. Possible decreasing of SERS substrate signal inside MSWs due to light absorbance and scattering on metal nanoparticles. Only disposable sensors are reported.
Luminescence spectrometry	
Intense signals, possibility to use both inherent luminescence of analytes and luminescence of labels. Possibility to use both stationary and pulse excitation regimes. Possibility to use both signal intensity or signal enhancement (decreasing) in the presence of target compound. Possibility of label-free detection of analytes with inherent luminescence.	Luminescence signal enhancement (decreasing) in MSWs could results in non-linear dependence of the target analytical signal on the concentration. Possible distortion (shifts) of luminescence signals. High risk of photobleaching of organic compounds.

Table 2

Microstructed waveguides based luminescent bioassay

Type of MSWs	Geometrical parameters*	Analyte	Detected Signal	LOD (detected level)	Conditions	Sample volume	Applicability of result	Ref.
DNA detection								
Silica glass SC MSWs	*A* = 10 μm, *L* = 7 cm (filling 4 cm)	Specific DNA sequences	Enhancement of molecular beacons luminescence λ_{Ex}=532 nm	4 μM	Fuzzy nanoassembly technique and the biotin-streptavidin binding			[63]
Immunochemical analysis								
Soft F2 glass SC MSW	*A* = 1.3 μm, *B* = 4.3 μm, *L* = 19.2 cm	Purified mouse IgG	Luminescence of Qdot800 goat F(ab')2 anti-mouse IgG conjungate λ_{Ex}=532 nm λ_{Em}=790 nm	(100 nM)	Functionalization of MSWs hole surface (3-mercaptopropyltrimethoxysilane/N-γ-maleimidobutyryloxy succinimide ester) and sequential immobilization of antibody and labeled IgG	-		[68]

Type of MSWs	Geometrical parameters*	Analyte	Detected Signal	LOD (detected level)	Conditions	Sample volume	Applicability of result	Ref.
Silica HC PCF (Crystal Fiber A/S–AIR-6-800).	*A* = 6 μm, *B* = 122 μm, *L* = 10 cm	Estrogen receptor (ERα) protein	Luminescence of green and red fluorescent dyes (Alexa™ Fluor) labeled goat anti-rabbit IgG λ_{Ex}=473(green), 532 (red) nm λ_{Em}=515 (green), 585 (red) nm	20 pg	Functionalization of the PCF hollow core (poly-L-lysine) and cell lysate immobilization.	50 nL	Medical diagnostic and therapeutic applications	[71]
Silicate soft glass (F2) SCW	*A* = 1.5 μm, *C* = 7.5 μm, *L* = 18 cm	Goat F(ab') anti-mouse IgG	Luminescence of CdTe/ZnS QDs labeled proteins λ_{Ex}=532 nm λ_{Em}=800 nm	1 nM	Filling of the fibers holes with sample via capillary forces.	10 pL		[72]

Type of MSWs	Geometrical parameters*	Analyte	Detected Signal	LOD (detected level)	Conditions	Sample volume	Applicability of result	Ref.
Polymer (TOPAS) SC MSW	*A* = 12 μm, *B* = 40 μm, *D* = 200 μm, *L* = 30 cm	Two antibodies: specific to streptavidin and C-reactive protein (CRP)	Luminescence of Cy3-labelled - specific to streptavidin antibody (λ_{Ex}=532 nm, λ_{Em} = 570 nm) and Cy5-labelled specific to-CRP antibodies (λ_{Ex} =532 nm, λ_{Em} = 670 nm)	-	Attaching of anthraquinone to the hole surface; sequential activation of the photolinker (UV light) and immobilization antigens in different sections of MSWs, probing with labeled antibody			[73]
Enzyme based analysis								
Silica SC MSW	*A* = 2.1 μm, *D* ~ 120 μm, *L* = 10.0 cm	Proprotein convertase 5/6 (PC6)	Appearance of 7-amino-4-methylcoumarin luminescence λ_{Ex}=372 nm, λ_{Em}=405 nm	50 U/mL	Pre-mixing the enzyme and peptide substrate.	210 nL	Minimally invasive and non-disruptive diagnostic tool for assessing endometrial receptivity.	[56]

* *L* is length of MSWs sample; for solid (suspended) core MSWs: *A* is the solid core diameter, *B* is the hole diameter, *C* is the strut length, *D* is outer fiber diameter; for HC MSWs: *A* is the hollow core diameter, *B* is the cladding diameter, *C* is the outer fiber diameter.

Captions to illustrations

Figure 1. Cross-section of commercially available solid core waveguides: microstructed solid core LPG waveguides [18] (a), nonlinear photonic crystal fibers with solid core [13] (b), large mode area photonic crystal fibers with solid core [13] (c), Kagome photonic crystal fibers with solid core [14] (d).

Figure 2. Cross-section of commercially available hollow core waveguides: hollow core microstructed waveguides [14] (a), HC PCFs [13] (b), Kagome with hollow core [13] (c).

Figure 3. The microphotograph of the cross section (a) and transmission spectrum (b) of the chirped microstructed waveguide. Hollow core diameter is 280 μm; thickness of the capillary walls is 2.5 μm.

Figure 4. A scanning electron microscope image of the cross-section of the SC MSWs and the schematic diagram of the final surface state of the MB functionalized. PAH - poly(allylamine) hydrochloride, PSS - poly(sodium 4-styrene sulfonate) [63]. Copyright 2012, with permission from The Optical Society.

Figure 5. Schematics of optofluidic platform and micrograph of defected-core photonic crystal fibers with schematics of coating assembly comprising a base layer bovine serum albumin (BSA), photobleached biotin-4-fluorescein (pbB4F) and Atto488-conjugated streptavidin (Atto488Strep) [64]. Copyright 2014 Society of Photo Optical Instrumentation Engineers.

Figure 6. Small-core microstructed optical fibers with a periodic triangular arrangement of cladding holes: A is the solid core diameter, B is the hole diameter, C is the strut length, D is outer fiber diameter.

Figure 7. Experimental setup for MSW spectral analysis: MO - microscope objective; FC - fiber coupler [71]. Copyright 2010 Society of Photo Optical Instrumentation Engineers.

Figure 8. Experimental setup for protein detection [72]. Copyright 2007, with permission from The Optical Society.

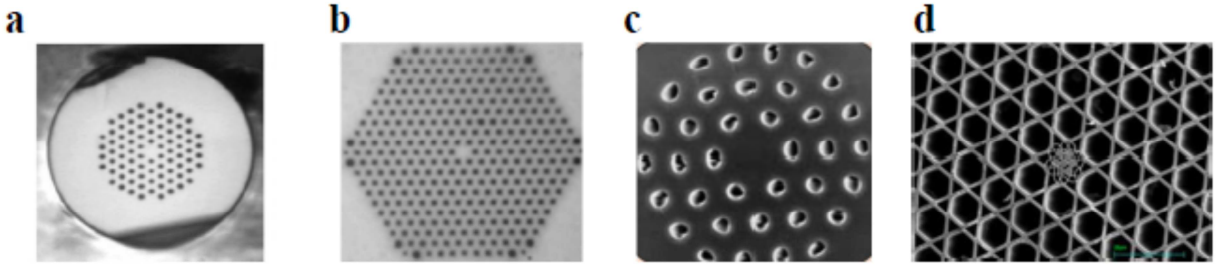

Figure 1

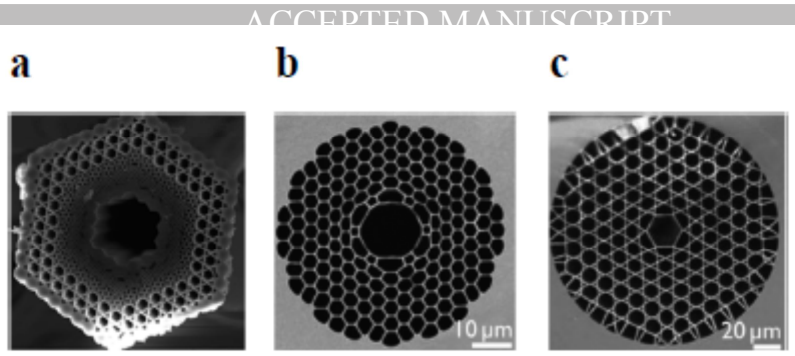

Figure 2

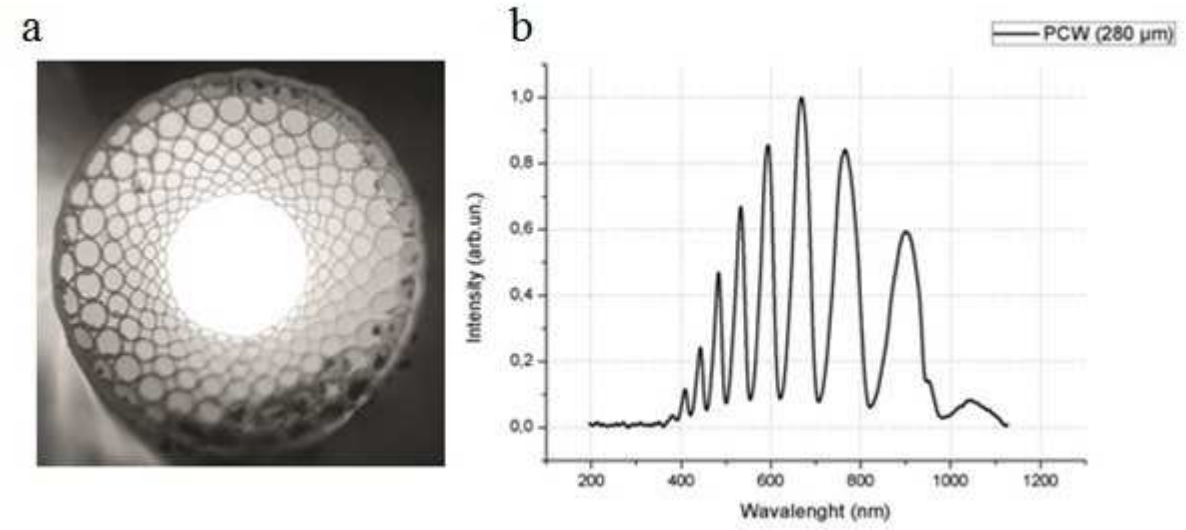

Figure 3

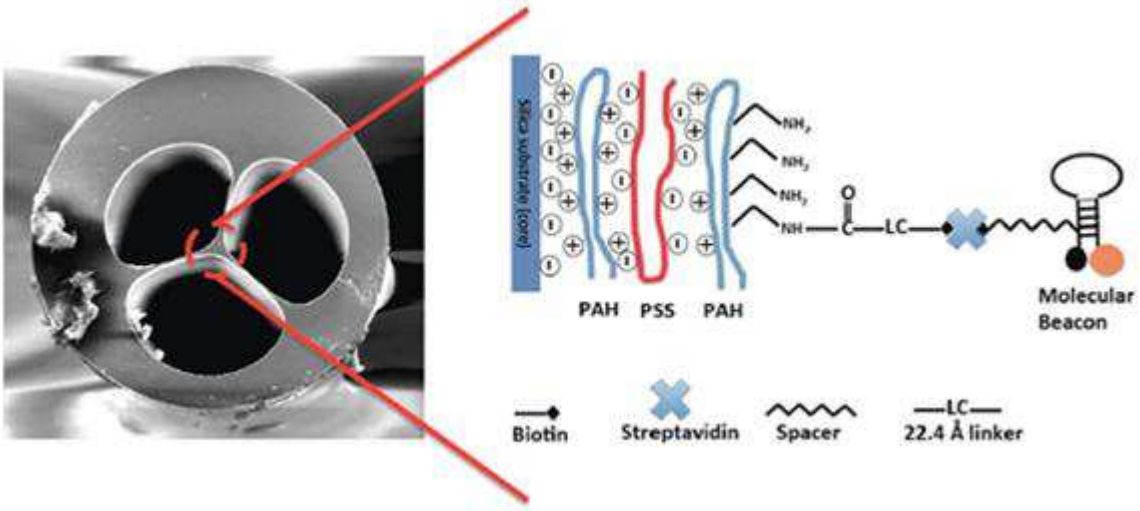

Figure 4

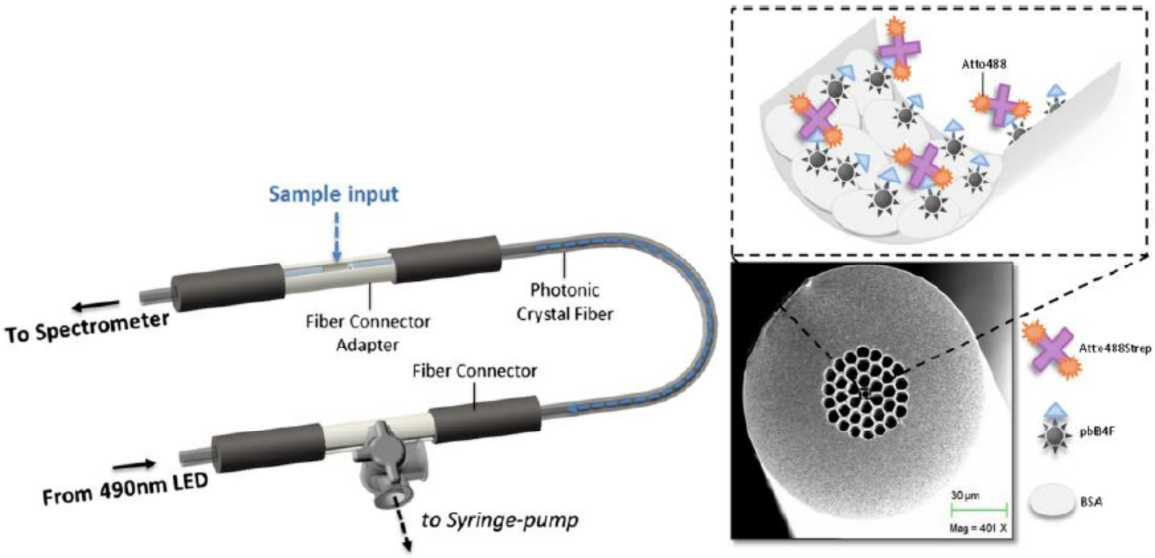

Figure 5

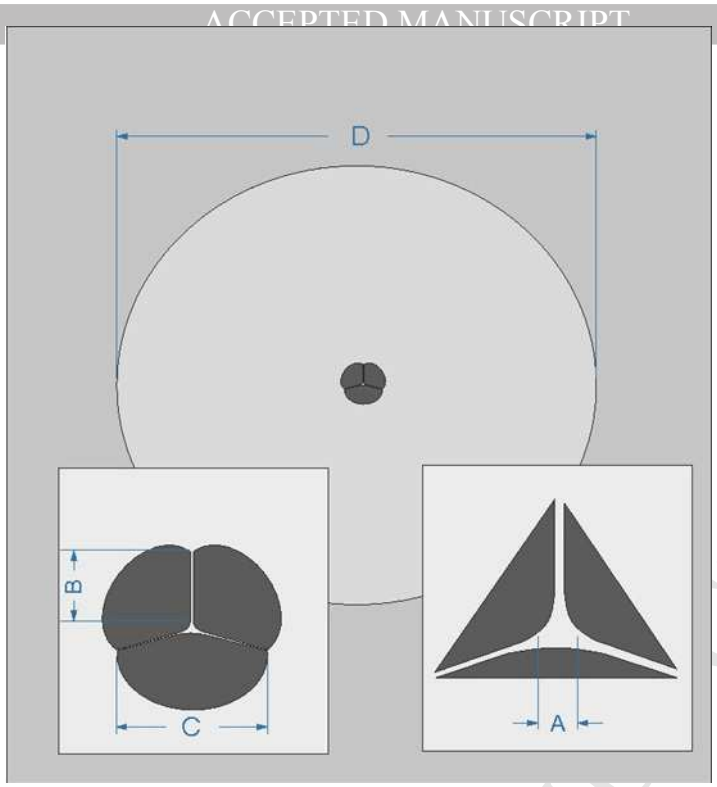

Figure 6

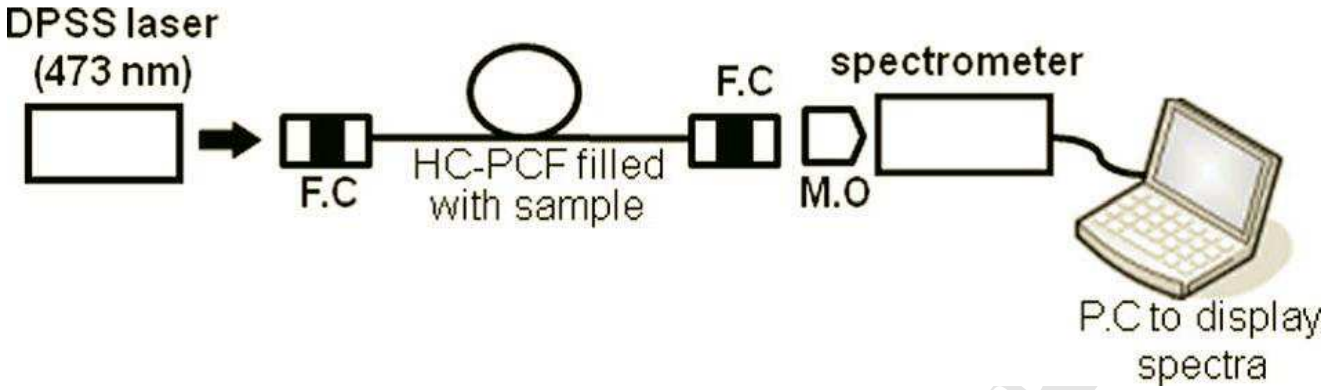

Figure 7

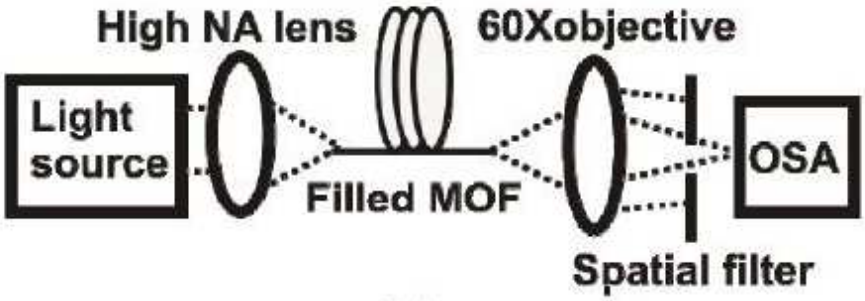

Figure 6

Highlights

- The luminescence detection in microstructed optical fibers (MSWs) is reviewed.
- Current trends of application MSWs for luminescence biosensing are discussed.
- Potential and limitation of MSWs based biosensors are analysed.

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