Nanoparticle Bragg reflectors: A smart analytical tool for biosensing

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\textbf{A B S T R A C T}

In this work, we present a novel optical biosensor based on periodically alternated layers of SiO\textsubscript{2} and TiO\textsubscript{2} nanoparticles grown by wet methods and working as a Bragg mirror in a label free format. The sensing principle relies on the change of the optical response generated by variations in the dielectric constant of the voids due to a biorecognition probe-target event. This change is reflected in a modification of the photonic band gap frequencies of the Bragg reflector. As a proof of concept, biotin and streptavidin biorecognition on the biosensor surface is monitored in label free format, achieving a LOD of 3.09 mgL\textsuperscript{-1} (54 nM) for the determination of streptavidin. Our proposed biosensor also shows selective determination against a variety of targets (horseradish peroxidase and bovine serum albumin antibody) working in physiological conditions (diluted human serum). To get a picture of the potential of our development and its ease of integration, we incorporated the immunosensor in an electronic consumable technology, such as compact disk, using the optical disk as analytical platform and a CD player detector for the determination of streptavidin. Thus, our findings point out the feasibility of nanoparticle based Bragg reflectors in the biosensing field and open new avenues towards the rational design of a new generation of versatile, easy to fabricate in mass scale and cost-competitive biosensors.

1. Introduction

Point-of-care diagnostics have awakened a great deal of attention of the scientific community and healthcare industry due to their potential for cheapening healthcare costs, enabling personalized diagnostic and bypassing time-consuming laboratory tests (Dincer et al., 2017; Nayak et al., 2017). An appealing approach with potential to meet many of the requirements of the ASSURED criteria of ideal features for a point-of-care test (Peeling et al., 2006; Ouyang et al., 2005), and different biosensing approaches since a comprehensive study of the sensing features of 1DPC mainly based on electrochemically etched porous silicon or alumina foil (Pacholski, 2007), within them, different biosensing approaches since affinity immuno- sensors to enzymatic biosensors have been developed for the systematic detection of different targets (Kilian et al., 2007; Orosco et al., 2006; Ouyang et al., 2005), and first attempt towards their commercialization was evoked by Bonanno et al. who validated the clinical detection of different opiates in urine (Bonanno et al., 2010). However, this type of Bragg reflectors presents several disadvantages such as the use of hazardous hydrofluoric acid for its fabrication, lack of reproducibility of pore size distribution, poor percolation of the biomolecules in their tube-shaped pores and instability of etched thickness of the layers. The connectivity of the pore network of the 1DPCs allows to occur the molecular event within the nanostructure, thus modifying the refractive indices of the layers and enabling its use for sensing purposes.

Since the conceptual demonstration by Snow at the late 90’s (Sailor, 2007; Snow et al., 1999), numerous groups have developed a comprehensive study of the sensing features of 1DPC mainly based on...
channel against solvents and functionalization. In this context, 1DPC architectures where films are processed by wet method deposition (dip-coating and spin-coating) of nanoparticle precursors, are very appealing sensing platforms, because they present advantages like, for example, the easy, reproducible and low-cost fabrication procedures, chemical robustness of mesoporous framework, the possibility to modulate the optical response through simple variations in the deposition conditions, larger active surface area which resulted in improved immobilization capacities and their feasibility to adapt to the morphology of different optical platforms (Colodero et al., 2008). Besides that, the employment of low temperature solution processed methods such as screen printing, dip coating, spin-casting or doctor blading, among others, has evolved to a promising manufacturing technology for fabricating light-weight and low-cost optoelectronic devices (Calvo et al., 2006; Sánchez-Sobrado et al., 2010).

Porous nanoparticle based 1DPCs offer the opportunity to act as base materials for sensing because of the interplay between porosity and optical properties, thus molecular targets retained in their mesoporous network will generate a perturbation of the optical response. They can be made with different materials such as metal oxide nanoparticle (TiO$_2$, SiO$_2$, SnO$_2$) or clays (laponite), and by this operation principle effective detection of alcohols, water and other volatile organic molecules have been reported (Bonifacio et al., 2010; Hidalgo et al., 2011). Nevertheless, as far as we know, they only have been exploited as vapor and small molecules non-selective chemical sensors. Herein, we described for the first time a biosensing approach based on the employment of solution processed nanoparticle 1DPCs built with alternated layers of SiO$_2$ and TiO$_2$ nanoparticles. In contrast to chemical and biological sensors, biosensor platforms enable the selective and sensitive detection of a myriad of analytes, because of the probe-target biorecognition properties. In particular, we tested the biosensor performance monitoring the optical response of biotin functionalized porous 1DPC produced by the selective attachment of streptavidin. Our nanoparticle-based 1DPC is a promising biosensing material because on the one hand contains a pore network that permits the free diffusion of biomolecules from outside and, on the other, can be specially designed to tune and maximize the spectral response for a given working wavelengths in the ultraviolet–visible and near infrared regions of the electromagnetic spectrum.

With the aim to inspect the versatility and capacity of our structures, the Bragg biosensors were also implemented in analytical systems based on compact disk technology. This biosensing modality exploits the operation principle and elements of audio-video technology to perform assays on regular discs (CD, DVD, BluRay) and to read the chemical results with a disk drive. CD technology drivers and supports measure withdrawal speed was set at 140 mm/s for both layers. Immersion time in the suspensions is 10 s and each layer is dried into the chamber during 30 s before to proceed with the next dip. A complete single layer is made by repeating the immersion 6 and 9 times in TiO$_2$ and SiO$_2$ suspensions respectively. The Bragg mirror was composed by three layers of TiO$_2$ (130 nm-thick) and two layers of SiO$_2$ (200 nm-thick). Samples are heated at 450°C in order to stabilize the layers and remove the polymeric porogocene and solvent traces. The structural characterization was performed by a JSM 5410 electron microscope (JEOL) operated at 2kV.

2.2. Surface functionalization

The photonic crystals (PC) underwent an oxygen plasma treatment for 10 min prior to surface functionalization. After oxidation, the inner surface of the photonic crystal was silanized with a 2% solution of 3-aminopropyltrimethoxysilane (APTES, Gelest) in toluene for 20 min. The amine derivatized substrates (PC–NH$_2$) were rinsed with toluene and ethanol and dried in a stream of nitrogen gas. The PCs were kept at 120°C for 1 h to evaporate any remaining solvents and to form crosslinks in the silane layer. Then, the biosensor surface was functionalized with biotin (PC-BT) by dipping in a 2 mg mL$^{-1}$ solution of N-hydroxysuccinimido-biotin (ThermoFisher) in DMF. The activated ester coupled with amine surface groups via amide bond formation. Variation of surface chemistry was monitored by water contact angle measurements, performed with a Data Physics system OCA equipment (Filderstadt, Germany).

2.3. Receptor and target chemistry

(i) Studies with labeled dyes. To estimate the density of streptavidin attached to the surface, probes with ATTO-655 labeled protein were performed. In this study different concentrations of streptavidin-ATTO655 (from 2.5 to 250 mg L$^{-1}$) in phosphate buffered saline (PBS$1 \times$) were printed on the surface as 40 nL drops with a non-contact array, creating a matrix of 1 × 4 spots for each concentration. The fluorescence intensity of the spots was registered before and after the washing using a home-made surface fluorescence reader featuring with a high sensitivity CCD camera (SFC reader). Fluorescence confocal microscopy characterization was made using a LEICA AOBSTS-SP2 microscope at 633 nm excitation and 670 nm emission laser lines, with a diode detector for interferential contrast (DIC), a motorized holder and an incubation chamber to regulate temperature. For selectivity assays, microarrays (2 × 6, 40 nL/slot, 100 mL/g) in PBS 1x) of HRP and streptavidin tagged with HRP were printed and incubated on biosensor and then revealed by tetramethylbenzidine.

(ii) Label free detection. The Bragg biosensor was incubated with...
increasing concentrations of streptavidin protein in PBS 1 × (ranging from 0 to 25 mg L$^{-1}$) for 40 min at room temperature and in a humidity chamber to allow diffusion of proteins within the pores. Then, surfaces were rinsed with PBS-T and deionized water and blown dry with N$_2$. Finally, after each incubation step the wavelength shifts of the transmittance peaks were monitored by means of UV–Vis diode array spectrophotometer (Agilent 8453). Measurements were carried out with a normal angle incident light and using an adjustable optical holder for an accurate alignment of the photonic crystals. For selectivity assays biotinylated 1DPCs were incubated with streptavidin as specific target, and horseradish peroxidase (HRP) and antiBSA as nonspecific targets. All incubations were performed at a biomolecule concentration of 5 mg L$^{-1}$ in normal human serum (3016626, Merck) diluted 1:10 (v/v) in PBS-T.

2.4. Bragg disk preparation

Commercial TED disks were purchased from MediaRange (MPO Iberica, Madrid, Spain). Bragg disks were made by assembling Bragg reflectors, grown on a cover slip by silicon elastomer (Sylgard 184, mixing ratio 1:10), on a high transmission TED disk. High transmission disk were prepared by eliminating the photochromic material, the protective layer, the metallic layer, and the recording dye of TED disk, keeping the original layered structure in the central control feature zone part. Photochromic and metallic layers were peeled off together by means of a blade-cut, and the recording dye layer was dissolved in an ethanol bath for 10 s at room temperature.

2.5. TED drive set up

The Bragg disks reading was carried out by a commercial disk drive (GSA-H55L, from LG Electronics Inc., Englewood Cliffs, USA). It has an optical pickup that simultaneously irradiates the disk surface with a 780 nm orthogonal laser source and collects the reflected beam. The pickup, disk rotor, and CFZ scanner are managed by a servo control system integrated in the standard drive. A 25.4 × 5.04 mm photodiode (SISD-71N6 from Silonex, Montreal, Canada) was incorporated above the disk and the laser beam for the transmission measurements. All light sensors (pickup, photodiode, and trigger photosensor) were connected to a data acquisition board (DAB, DT9832A-02- OEM from Data Translation Inc., Menlo Park, CA, U.S.A.) that collects analog signal,
digitalizes it, and transfers data to a computer through a USB2.0 connection. Disk irradiations were managed by Nero CoverDesigner software. When scanned data is transferred from drive to computer, custom C++ based software collects the signals from the photodiode and computes them, together with the photosensor signal, for arranging this into numerical data. Extensive details about TED drives analytical set up is documented elsewhere (Avella-Oliver et al., 2016, 2014).

3. Results and discussion

3.1. 1D-photonic crystal features

As displayed in Fig. S1, the spectral position of the Bragg peak of 1DPCs grown by wet methodologies can be tuned from blue to near-infrared by the adjustment of processing parameters. Strict control over the structural parameters yields multilayers in which the forbidden gaps can be devised as a minimum in the transmittance spectra. This allows tailoring the optical response of the ensemble to create 1DPCs “à la carte” and customize manufacturing according to measurement conditions, i.e. light source wavelength, detector and analytical platforms features. The pore size and porosity of these systems are dictated by the packing of the deposited particles. For this reason, the modification of both parameters is related with the change of the nanoparticle size, shape or with the inclusion of a porogene (normally high molecular weight polymers) (López-López et al., 2012).

Here in our work, as a demonstration of the potential and versatility of these porous nanostructures we constructed a photonic crystal to be implemented in an analytical system based on compact-disk technology, which adapts disk drives technology for optical readout of molecular biorecognition events on regular optical disks. In this set up, the light source comes from the laser pick up of the disk drive, which operates at 780 nm and principle of measurement is based on light transmittance variations upon target recognition (Fig. 1a). Therefore, a photonic structure which presents a PBG knee point at 780 nm wavelength) per percentage of protein surface coverage. For calculations we assumed an average porosity of 0.45 and 0.55, for TiO2 and SiO2 films, respectively. We included in the colloidal suspension of TiO2 particles a certain amount of porogene (polyethylene glycol, 50% of total TiO2 solids) with the aim to obtain open-access and pore connected structures. The good agreement between experimental and theory reflectance spectra is displayed in Fig. 1b and proves the concordance of simulation and experimental data.

We also simulated the PBG shift after APTES and NHS-Biotin functionalization steps (Fig. S3) and predicted an optical sensitivity for detection of biotin-streptavidin coupling of 1.7 nm spectral shift and 5.2% transmittance increase (for λ = 780 nm wavelength) per percentage of protein surface coverage. For calculations we assumed an average porosity of 0.45 and 0.55, for TiO2 and SiO2 nanostructured layers, respectively, and a protein molecular volume of 4.2 × 4.2 × 5.6 nm³ (van Oss et al., 2003; Williams et al., 2012).

3.2. Investigation of the target binding and specificity of linking chemistry

To evaluate the biosensing performance of the designed 1DPC, streptavidin-biotin coupling was selected as a model. Photonic crystals were functionalized with biotin, following the method described in Fig. 2. In brief, after plasma activation bare platforms were silanized with 3-aminopropyltriethoxysilane (APTES) to introduce amine groups on the surface (PC–NH₂). Alkoxy silanes have been extensively used for functionalization of hydroxylated surfaces, because of their well-developed chemistry and facility to introduce different chemical moieties. Next, biotin receptors were introduced by N-hydroxysuccinimidobiotin treatment, which reacts efficiently with amine groups to form stable amide bonds. The success of the chemical treatment was corroborated by measuring water contact angle (WCA) changes at different reaction stages. After oxygen plasma treatment, the surfaces became super-hydrophilic (θWC < 10°), which is in good correlation with the values reported in the literature and it is attributed to efficient surface
hydroxylation (Rosso et al., 2008). PC–NH2 shows a significant contact angle increase (θPC-NH2 = 68.7° ± 1.0°) due to the hydrophobic nature of aliphatic chains in APTES, whilst the water contact angle decreased to 35.1° ± 0.8° following biotinylation step. This decrease arises from the polar ureido- and tetrahydrothiophene-rings of biotin, which possess a hydrophilic nature (Williams et al., 2012).

The streptavidin nanostructure coverage density and the selectivity of bio-recognition event was investigated by means of a series of test with streptavidin labeled with ATTO 655, (λemission = 684 nm). With this purpose, the bare (PC) and functionalized (PC-BT) photonic crystals were incubated with streptavidin solutions. Confocal Fluorescence Microscopy (CFM) pictures shown in Fig. 2, reveals remarkably higher fluorescence intensity for biotinylated surfaces, thus confirming the success of the selective biotin-streptavidin attachment within the porous photonic crystal structure. Besides that, in Fig. 2 is also displayed the CFM image of the magnified cross section of biotinylated samples after protein incubation. The uniform luminescence observed along the mesoporous film points out that protein has diffused to deeper layer of the porous nanostructure instead of keep retained on top layers due to pore size spatial restrictions.

The target capture density was also determined by standard calibration curve, plotting fluorescence intensity against amount of spotted probe. For this purpose protein was spotted (1 × 4 microarray, 40 nL/spot, 0–250 mg L−1) on biotin active substrates with a noncontact dispenser onto investigated surfaces and fluorescence was recorded by SFC reader before and after washing step (Fig. S4a). With this method, the protein densities attained were of 6 × 10−7 g cm−2 (11 pmolcm−2). It is remarkable the higher density of linked protein presented by our method, increase over the previously mentioned literature for mesoporous silicon based biosensors (1–2 μM) (Bonanno and DeLouise, 2007; Ouyang et al., 2005) and only overpassed by 1D photonic structures fabricated by sputtering or lithography methods which are expensive, time consuming and require skill operators (Jahns et al., 2015). It is remarkable that no significant shift is observed for control assay where PC-BT were treated with buffer solution (i.e. in the absence of protein), indicating very little contribution of the remaining solvent molecules in the optical response.

In order to evaluate the selectivity of the streptavidin-biotin binding attachment in physiological medium, the 1DPCs were incubated with HRP enzyme, which is a protein with similar hydrodynamic radius and structural properties of SA, and streptavidin protein labeled with horse radish peroxidase (HRP-HRP). After washing, the samples were treated with tetramethylbenzidine, and HRP substrate produces a blue precipitate. As could be appreciated in Fig. S4b, spots treated with SA-HRP exhibit a dark blue color whilst the ones treated only with the enzyme features a light blue color due to spontaneous oxidation of the substrate by light (Volpe et al., 1998), hence, corroborating specificity of the biomolecular recognition.

3.3. Label free detection

Taking into account the operation working principle of photonic crystals, molecular events occurring in the mesopores produce a variation of the dielectric permittivity, modifying the spectral position of the Bragg peak. Variations in the optical response after chemical modification were monitored and are depicted in Fig. 3b. Spectral wavelength shifts of 21.0 ± 3.4 nm and 8.7 ± 3.9 nm were registered after amine and biotin functionalization, respectively (data given for the average of seven different samples prepared in different days). It is worth to note that these results further confirm the successfully and reliable chemical modification of the studied substrates. Moreover, control experiments in which samples were treated with solvents in absence of chemicals (Fig. 3a) allow us to rule out the contribution of the remaining solvent molecules in the voids of the pore structure that will modify the optical response of the 1DPC.

For the sensing of the biotin-streptavidin biorecognition reactions, PC-BT nanostructures were incubated with increasing concentrations of protein in PBS 1×. After each incubation step the samples were rinsed with PBS 1× and thoroughly blown with N2. Further, removal of remaining water was performed by mild heating treatment. The red-shift of the spectrum upon exposure to streptavidin is shown in Fig. S5, whilst spectral shifts and percentages of transmission increase at 780 nm versus protein concentration are summarized in Fig. 4 (a and b) and Table S1.

The Bragg mirror exhibits sensitivities of 1.81 ± 0.26 nm/(mg·L−1) (spectral shift) and 1.01 ± 0.14% transmittance increase at λ = 780 nm wavelength for streptavidin determination and a limit of detection of 3.09 mg L−1 (54 nM). In respect with 1D photonic crystals, our LOD for streptavidin target is significantly lower than reported in literature for mesoporous silicon based biosensors (1–2 μM) (Bonanno and DeLouise, 2007; Ouyang et al., 2005) and only overpassed by 1D photonic structures fabricated by sputtering or lithography methods which are expensive, time consuming and require skill operators (Jahns et al., 2015). It is remarkable that no significant shift is observed for control assay where PC-BT were treated with buffer solution (i.e. in the absence of protein), indicating very little contribution of the remaining solvent molecules in the optical response.

3.4. Sensing on Bragg-disk platform

Here we present a hybrid platform composed by 1D-PCs integrated in a TED analytical disk, referred as Bragg-disk, for label free protein detection. TED disks and LightScribe technology was conceived as a disk labeling tool through laser etching of a serigraphy layer on disk surface, and hence, TED controls the pickup course by continuously irradiating a circular coordinate code situated in the inner part of the disk, control feature zone. Accordingly, contrary to CD, DVD and Blue ray optical systems, where size, shape and chemical disk properties matters in the drive optical reading (i.e. disruption of the track irradiation and abort of the scanning process), TED technology enables the
selective irradiation of the assay surface, and therefore the design and development of truly integrated analytical systems (Avella-Oliver et al., 2016, 2014).

For this purpose, TED disks, were modified by peeling off the original metallic and protective layer. The resulting disks were 1.3 mm-thick polycarbonate platforms which preserves their inner annulus, control featured zone that encodes pick up irradiation position on disk surface. After, Bragg-disks were constructed by assembling 1D-PCs grown onto a coverslip (0.15 mm-thick). PCs were adhered to TED disks by means of PDMS elastomer (Sylgard 184) (Fig. 5a). In this analytical system the molecular recognition events on disk surface will alter the interference pattern of PCs, triggering changes in the transmission of the disk laser drive through the analytical platform. The intensity variations of light laser beam are measured by using the developed reading device (see experimental section). A scheme of the TED drive analytical setup is provided in Fig. 5b. It is important to note that the laser wavelength used by this system is \( \lambda = 780 \text{ nm} \) and the detection is made by transmittance. This setup arrangement justifies the values of reflectance and maximum spectral position of the designed Bragg mirror whose optical performance were aforementioned.

For streptavidin detection biotin activated surfaces PC-BT were incubated for 40 min with increasing protein concentration solutions. Then the surface was rinsed with PBS 1 × and blown with N2, and then the disks were read. Fig. 5c displays the light collected by the photosensor upon irradiation of PCs structures which half of their surface have been incubated with streptavidin (1 mg L\(^{-1}\)) (lower graph) and their untreated counterparts (upper graph). From this figure is noteworthy the transmittance heightening observed for nanostructure treated with protein, addressed to PBG fringes displacement due to biomolecular recognition. Transmittance increase registered upon streptavidin concentration is plotted in Fig. 5d. Although proposed Bragg Disk platforms are in good correlation with previous data of 1DPCs grown on glass substrates, it is remarkably that they present narrower dose-response linear range which reduces the interval of working concentrations, as well as lower sensitivity (0.64 ± 0.07 \( \Delta T/ \text{mg L}^{-1} \)) and LOD (0.87 mg L\(^{-1}\)) in respect to their glass counterparts. Such differences between both systems may arise from different optical set up features, such as laser spot light diameter and power of the light source.

It is worth to note, that despite CD based platform is a mature technology with proven guarantees, they suffer from the need of labeling agents which drives up the final costs and very often are problematic because the labeling molecule may occupy an important binding site or cause steric hindrance, resulting in false information regarding interactions (Cooper, 2009). In this sense, the development of label-free technologies based on compact-disk platforms is being for years the Holy Grail in the field of disk-based analytical systems. Along these lines, there are some reported approaches based on label-free disks which employ highly sophisticated supports and drives (Barrios et al., 2014; Gopinath et al., 2008). Herein, is reported a label free detection approach based on CD technology and maintaining optical drive and disk platforms. This strategy presents a great potential to provide compact and portable platforms for biosensing approaches at point-of-care for the rapid, on-site, and label-free detection of chemical targets and biotargets.

4. Conclusions

In this study we demonstrate a new label-free biosensing strategy based on 1DPCs nanostructures fabricated by wet chemical synthesis of colloidal SiO\(_2\) and TiO\(_2\) nanoparticles. A mesoporous Bragg mirror with predefined optical properties was fabricated by dip-coating of nanoparticle precursors, silanized and activated with biotin receptors. Biorecognition assays using fluorescent labeled streptavidin confirm the
effectiveness of the functionalization and the biotin-streptavidin specific recognition.

In a label free format our biotin decorated 1DPCs exhibit sensitivities of 1.81 ± 0.26 nm/(mg·L\(^{-1}\)) (spectral shift) and 1.01 ± 0.14 (transmission increase at 780 nm) and a limit of detection for protein of 3.09 mg L\(^{-1}\). This latter goes beyond the state of art of their mesoporous silicon etched counterparts. In addition, selectivity studies, corroborate the specificity of the biological binding and the minor unspecific attachment in this assay conditions, even after incubation of our platforms with a cocktail solution, including a variety of target probes (HRP and antiBSA), and working in physiological conditions (diluted human serum).

The developed approach presents many attractive features to infer in the biosensing field, such as, the ease and low cost manufacture, the feasibility to integrate 1DPCs in different device architectures, label free detection and the possibility to envisage the biosensor photonic response by simple synthetic variation, which endow the fabrication of a collection of biosensing nanostructures with different optical response.

Going one-step forward, the 1DPCs were integrated on TED analytical platform, Bragg-disk, and even lower detection limits (0.87 mg L\(^{-1}\)) were obtained for streptavidin screening by this optical set up. The proposed Bragg Disk biosensor enables label free detection by means of easily customized disks and CD detectors, as opposed to label free disk technologies in literature, which depend on expensive and sophisticated supports, and detectors. In addition, our work constitutes a smart analytical tool, which couples the usefulness of compact disk technology analytical features, such as, robustness, ubiquity, portability, possibility to automatize the assay and high quality/price ratio of the optical drive, as well as the benefits of photonic nanostructures.

Finally, it is noteworthy that although nanoparticle Bragg reflectors are multi-facet materials whose technological potentiality has been extensively demonstrated in different fields, mainly in photovoltaics, up to date their biosensing capabilities have not been investigated. For all these reasons, our work sets the starting point towards the development of nanoparticle 1DPCs biosensors. Nevertheless, further future investigations to address their main limitations, such as the study of more open-access structures, which facilitates analyte percolation and increases sensitivity, and expansion of our biosensing platforms to other biorecognition systems, are mandatory towards the design of nanoparticle 1D photonic crystals with potential to provide solutions within the point-of-care framework.

CRediT authorship contribution statement

Victoria González-Pedro: Investigation, Formal analysis, Methodology, Writing - original draft. Mauricio E. Calvo: Investigation, Formal analysis, Writing - review & editing. Hernán Míguez: Conceptualization, Writing - review & editing. Ángel Maquieira: Conceptualization, Investigation, Funding acquisition, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biosx.2019.100012.

Notes

The authors declare no competing financial interest.
Declaration of interests

- The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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