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A photoelectrochemical immunosensor based on magnetic all-solid-state Z-scheme heterojunction for SARS-CoV-2 nucleocapsid protein detection

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ABSTRACT

Rapid, convenient and accurate detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is urgently needed to timely diagnosis of coronavirus pandemic (COVID-19) and control of the epidemic. In this study, a signal-off photoelectrochemical (PEC) immunosensor was constructed for SARS-CoV-2 nucleocapsid (N) protein detection based on a magnetic all-solid-state Z-scheme heterojunction (Fe3O4@SiO2@TiO2@CdS/Au, FSTCA). Integrating the advantages of magnetic materials and all-solid-state Z-scheme heterostructures, FSTCA was implemented to ligate the capture antibody to form magnetic capture probe (FSTCA/Ab). It can simplify the separation and washing process to improve reproducibility and stability, while allowing immune recognition to be performed in the liquid phase instead of the traditional solid-liquid interface to improve anti-interference. Besides, the heterojunction inhibited the recombination of photogenerated electron/hole (e−/h+) and promoted the light absorption to provide superior photoelectric substrate signal. The mechanism of photogenerated e−/h+ transfer of FSTCA were investigated by the electron spin resonance (ESR) spectroscopy. SiO2 spheres loaded with Au NPs utilized as an efficient signal quencher. The steric hindrance effect of SiO2@Au labeled detection antibodies (SiO2@Au-Ab2) conjugates significantly diminished light absorption and hindered the transfer of photogenerated electrons, further amplifying the signal change value. Based on the above merits, the elaborated immunosensor had a wide linear range of 10 pg mL−1–100 ng mL−1 and a low detection limit down to 2.9 pg mL−1 (S/N = 3). The fabricated PEC immunosensor demonstrated strong anti-interference, easy operation, and high sensitivity, showing enormous potential in clinical diagnosis of SARS-CoV-2.

1. Introduction

The COVID-19 caused by the SARS-CoV-2 has caused great damage worldwide and was declared a pandemic by World Health Organization (WHO) on 11 March 2020 [1,2]. According to WHO, as of 5:10 pm CEST, 9 June 2022, there had been 531,550,610 confirmed cases of COVID-19. SARS-CoV-2 nucleocapsid (N) protein is a structural protein of SARS-CoV-2, which is used to promote viral replication and assembly release [3]. Due to its strong immunogenicity, stability and abundant expression during infection, SARS-CoV-2 N protein can be used as a good biomarker for SARS-CoV-2 [4]. Several papers on the detection of SARS-CoV-2 N protein have been published. For example, Bradbury et al. [5] developed a 3D-printed casing based on lateral-flow immunoassay (LFA) to detect SARS-CoV-2 N protein in 40 min. Cai et al. [6] presented duplex digital enzyme-linked immunosorbent assay (dELISA) to detect N protein with detection limit of 69.8 fg mL−1. Liu et al. [7] constructed a HRP-labeled fluorescent immunoassay platform to evaluate SARS-CoV-2 N protein level in serum. However, most LFAs provide only qualitative rather than quantitative results. The other methods usually require professional operators and expensive equipment. Consequently, rapid, convenient and accurate detection methods of N protein are essential for the diagnosis of SARS-CoV-2 and further control the epidemic.

The photoelectrochemical (PEC) immunosensor is the synergy of photoelectrochemical detection and immunoassay with complementary advantages [8]. Immunomolecules have bioaffinity and biocompatibility properties, which provide superior specificity for the sensor [9]. The separation strategy of excitation source (light) and detection signal (current) offers low background signal for PEC immunosensor [10]. Meanwhile, as an advanced version of electrochemical immunosensor,
PEC immunosensor inherits its characteristic of low cost and easy operation. PEC immunosensor had gathered tremendous attention due to the above reason recently [11,12]. In PEC immunosensor, the concentration change of target detection is transmitted through the change of electrical signal generated by semiconductor materials. Unfortunately, traditional semiconductor materials are difficult to meet the increasing demands of PEC immunosensor. On the one hand, the process of immune sensing based on traditional semiconductor materials is complicated, and the immune process of electrode surface is interfered by the inherent absorption of solid-liquid interface [13]. On the other hand, most traditional single-phase semiconductors only display unsatisfactory initial photocurrent signals due to their low photoelectric conversion efficiency [14]. Therefore, it is urgent to design and synthesize a new photoelectric material that can simplify experimental steps and provide prominent PEC response.

Magnetic nanoparticles ferroferic oxide (Fe$_3$O$_4$) attracted great attention due to its easy separation, good biocompatibility, and simple synthesis, while the easy agglomeration of Fe$_3$O$_4$ limited its application [15]. Coating inert SiO$_2$ layer on Fe$_3$O$_4$ surface to form core-shell structure Fe$_3$O$_4$/SiO$_2$ (FS) can prevent its agglomeration and ameliorate its stability. The application of FS with magnetic affinity in PEC immunosensor can reduce the amount of sample processing and avoid the interference of inherent absorption at solid-liquid interface. Hence, FS can be used as an appropriate choice to be introduced into semiconductor materials.

Among semiconductor materials, titanium dioxide (TiO$_2$) is frequently used as a photoelectric basic material due to its strong light absorption, good biocompatibility, and low cost [16]. Magnetic TiO$_2$ (Fe$_3$O$_4$/SiO$_2$/TiO$_2$, FST) produced by functionalizing TiO$_2$ with FS possesses dual advantages of TiO$_2$ and magnetic nanomaterials. However, as a single photoelectric active component in FST, TiO$_2$ has the disadvantage of easy recombination of photogenerated electron/hole (e$^-$/h$^+$). Constructing heterojunction is an effective approach to improve this drawback [17]. Compared with the traditional type-I and type-II heterojunction, the all-solid-state Z-scheme heterojunctions has a unique electrons transfer mode and introduced electron transfer media [18]. The electrons in the conduction band (CB) of the semiconductor combine with the holes in the valence band (VB) of another semiconductor through electron medium directly and rapidly. This electrons transfer mode not only improves the photoelectric conversion ability but also retains high redox ability [19]. With narrow band gap (2.4 eV vs. NHE) matching TiO$_2$ band gap, cadmium sulfide (CdS) can be an applicable candidate [20]. Au NPs can enhance the visible light absorption and accelerate the transfer of electrons. In summary, CdS and Au NPs are suitable for combining with FST to form heterojunctions to provide outstanding photoelectric substrate signal.

In this work, we synthesized magnetic all-solid-state Z-scheme heterojunction (Fe$_3$O$_4$/SiO$_2$/TiO$_2$/CdS/Au, FSTCA) by coating a composite layer that consists of TiO$_2$, CdS, and Au NPs on FS and applied it to construct a PEC immunosensor for the quantitative detection of SARS-CoV-2 N protein. FSTCA exhibits excellent magnetic enrichment properties, and its application simplifies the electrode treatment process and enables immune recognition performed in liquid phase. The heterojunction effectively separates photoproduced e$^-$/h$^+$, providing outstanding photoelectric conversion capability. Electron spin resonance (ESR) detection of active free radicals was used to explore the mechanism of photoproduced e$^-$/h$^+$ transfer of FSTCA. The steric hindrance of SiO$_2$@Au–Ab$_2$ conjugates significantly weakened light absorption and hindered the transfer of photogenerated electrons. The constructed PEC immunosensor displays a competitive method for SARS-CoV-2 N protein determination.

### 2. Experimental section

Details of reagents, apparatus, synthesis of FSTCA, synthesis of SiO$_2$@Au, and PEC detection conditions were listed in [Supplementary material](#).

#### 2.1. Preparation of FSTCA/Ab$_1$ and SiO$_2$@Au–Ab$_2$ conjugates

Preparation of FSTCA/Ab$_1$: FSTCA (3 mg mL$^{-1}$, 5 mL) was washed with PBS by magnetic separation, and the supernatant was discarded. 5 mL of 200 μg mL$^{-1}$ 2D3 (Ab$_1$) was added and shaken for 12 h at 4°C. FSTCA/Ab$_1$ was washed and extracted by magnetic separation. Then, it was blocked by 1% BSA (w/v) at 4°C for 1 h, and the solution was washed with PBS buffer. Afterward, conjugates FSTCA/Ab$_1$ were dispersed in 5 mL of PBS buffer.

Preparation of SiO$_2$@Au–Ab$_2$: SiO$_2$@Au (5 mL) was washed with PBS, discard the supernatant. 5 mL of 200 μg mL$^{-1}$ 3F2 (Ab$_2$) was added and shaken for 12 h at 4°C. After centrifugation and washing, it was blocked by 1% BSA (w/v) at 4°C for 1 h. SiO$_2$@Au–Ab$_2$ conjugates were dispersed in 5 mL of PBS for storage after centrifugation and washing.

#### 2.2. Formation of immune complexes and PEC detection

Initially, SARS-CoV-2 N protein (500 μL) with various concentrations (0.01, 0.1, 1, 10, and 100 ng mL$^{-1}$) was added into 500 μL of FSTCA/Ab$_1$ precipitation and then incubated at 37°C for 1 h, and PBS buffer was used as blank sample. Subsequently, FSTCA/Ab$_1$/BSA/SARS-CoV-2 N protein was washed to remove unbound SARS-CoV-2 N protein by magnetic separation, SiO$_2$@Au–Ab$_2$ (500 μL) was added and incubated at 37°C for 1 h. The conjugation was dispersed in 500 μL PBS after washed by magnetic separation. Finally, 15 μL of the product was cast on the indium tin oxide (ITO) electrode and dried at 25°C, followed by photocurrent test. Scheme 1 showed the preparation process of FSTCA (A) and PEC immunosensor (B).

### 3. Results and discussion

#### 3.1. Characterization of FSTCA composite

The TEM images revealed that Fe$_3$O$_4$ presented a uniform spherical shape with an average diameter about 180 nm (Fig. 1A). In order to improve the stability of the magnetic core and the lattice mismatch between Fe$_3$O$_4$ and TiO$_2$, a layer of SiO$_2$ was coated on the surface of Fe$_3$O$_4$ by sol-gel method. Compare with single Fe$_3$O$_4$ sphere, the material surface was smooth and the protective layer was about 25 nm thick (Fig. 1B). As shown in the Fig. S1A, after the TiO$_2$–CdS–Au NPs were translated into Fig. S2A, B, and C by Digital software. The TEM images revealed that the SiO$_2$ layer was about 25 nm thick (Fig. 1B). As shown in the Fig. S1A, after the TiO$_2$ layer was coated on the surface of FS by sol-gel method, the uniform size of FST was about 350 nm. In order to obtain highly crystalline TiO$_2$ layer to improve photoelectric conversion performance, the as-obtained powder was calcined in air at 500°C for 2 h. In Fig. 1C and Fig. S1B, the mean diameter of material after calcination was about 290 nm. The decrease of the thickness may be attributed to the micro corrosion of SiO$_2$ layer by ammonia and the high temperature leaded to the densification of the TiO$_2$ layer [21]. An oil bath method was executed to synthesize FSTCA, the thickness of the CdS layer was about 10 nm (Fig. 1D). Fig. 1E and Fig. S1C exhibit that Au NPs were successfully loaded on the surface of FSTCA by in-situ synthesis. The lattice fringes of TiO$_2$, CdS, and Au NPs can be observed by high-resolution TEM (Fig. 1F). The lattices of TiO$_2$, CdS, and Au NPs were translated into Fig. S2A, B, and C by Digital Micrograph software. The results presented interplanar lattice spacing of 0.35 nm, 0.33 nm, and 0.23 nm, which were matched with TiO$_2$ (101) [22], CdS (111) [23] and Au (111) [24], respectively. As revealed in Fig. 2G, SiO$_2$ spheres had good dispersion and uniform particle size, with an average diameter of 230 nm. Au NPs with a particle size of about 10 nm were loaded on the surface (Fig. 1H, J, K). The results of EDS (Fig. S3) and elemental mappings (Fig. 1I) showed that the materials contained Fe, Si, Ti, Cd, S, and Au elements.

To further understand the surface composition and valence state of FSTCA, XPS measurement was carried out on FSTCA. The survey spectra indicated that the existence of Si, Ti, Cd, S, and Au elements...
The characteristic binding energy of Fe 2p was not found in the XPS spectra, which was attributed to the fact that XPS can only measure the distance of about 10 nm from the sample surface and that the FeO₄ core was coated with a thick shell too far from the particle surface [25]. The peak at 102.38 eV corresponded to Si 2p (Fig. 2B) [26]. In Fig. 2C, the Ti 2p spectrum of FSTCA comprised two peaks with different binding energies of 458.70 eV and 464.39 eV, which corresponded to Ti 2p₃/₂ and Ti 2p₁/₂, respectively [27]. The XPS spectrum of Cd of pristine CdS can be deconvolved into two peaks, including Cd 3d₅/₂ (405.27 eV) and Cd 3d₃/₂ (412.02 eV) (Fig. 2D), and the XPS spectrum of S of pristine CdS can be divided into two peaks S 2p₃/₂ (161.55 eV) and S 2p₁/₂ (162.76 eV) (Fig. 2E) [28]. The peaks of 84.01 eV and 87.67 eV in the Au 4f spectrum corresponded to Au 4f₂/₅ and Au 4f₇/₈ (Fig. 2F) [29]. According to the XPS results, it is confirmed that the FSTCA was successfully synthesized.

Fig. 3A displays the XRD pattern for F, FS, FST, FSTC, and FSTCA. The characteristic peaks at 21.25°, 35.09°, 41.37°, 50.44°, 62.89°, 67.23°, and 74.10° were assigned to the (111), (220), (311), (400), (422), (511), and (440) planes of the magnetite Fe₃O₄ (JCPDS 19-0629). Compared with pure Fe₃O₄, FS had a broad peak at 20–30° corresponding to SiO₂ (JCPDS 29-0085) was observed, indicating that the amorphous SiO₂ shell was successfully coated. Herein, the diffraction peaks at 29.44°, 45.11°, 56.43°, and 64.92° corresponded to the (101), (112), (200), and (211) planes of the TiO₂ (JCPDS 21-1272). The diffraction peaks of CdS and Au nanoparticles were not observed in the XRD pattern of FSTCA, probably due to their low content in the composite.

The magnetic hysteresis loops were measured to evaluate the magnetic properties of F, FS, FST, FSTC, and FSTCA at room temperature (Fig. 3B). The magnetic saturation (Ms) value of pure Fe₃O₄ was approximately 60 emu g⁻¹. With the SiO₂ coated on Fe₃O₄, the Ms reduced to 39 emu g⁻¹ due to the nonmagnetic shell of SiO₂. After successful coating of TiO₂ and CdS layer, the Ms decreased to 26 emu g⁻¹ and 20 emu g⁻¹. After in-situ formation of Au NPs on FSTC surface, the Ms further decreased to 18 emu g⁻¹, which indicated FSTCA has strong magnetization.

3.2. Photoelectrochemical performance and possible mechanism

UV-vis diffuse reflection spectra were utilized to characterize the light absorption performance of FST, FSTC and FSTCA. From Fig. 3C, the absorption edges of FST, FSTC, and FSTCA were located at 680 nm, 710 nm, and 745 nm, respectively. It indicated that CdS and Au NPs co-sensitized composites exhibited wider absorption range and higher light utilization.

Fig. 3D shows the photocurrent response of the FST, FSTC, and FSTCA. The photocurrent of FSTCA was significantly enhanced compared with FST, which can be attributed to the following two reasons: the well-matched band structures promoting photogenerated charge separation and the excellent conductivity of Au NPs accelerating the transfer of photogenerated electrons.

To elucidate the mechanism of photocurrent increase of FSTCA, ESR spectra (Fig. 4A, B) were used to identify the active intermediates and infer the possible photogenerated e⁻/h⁺ transfer channel. The presence of hydroxyl radicals (·OH) and superoxide radicals (·O₂⁻) was confirmed by using 5,5-dimethyl-1-1-pyrroline N-oxide (DMPO) as the capture agent [30]. Signals of both DMPO–O₂ and DMPO–·OH are clearly observed under visible light illumination, but no obvious signal can be detected in the dark, which proves that ·O₂⁻ and OH are produced under light condition.

Fig. 4C shows the tentative photogenerated e⁻/h⁺ transfer pathways of FSTCA. If the photogenerated e⁻/h⁺ transfer pathway conforms to the type-II heterojunction (a), the electrons on the CB of CdS transfer to the CB of TiO₂, and the holes on the VB of TiO₂ transfer to the VB of CdS, resulting in the accumulation of electrons on the CB of TiO₂ and holes on the VB of CdS. However, the potential of CB of TiO₂ (–0.29 eV vs. NHE) [31] was less negative than that of O₂/·O₂ pair (–0.33 eV vs. NHE) [32], the potential of VB of CdS (–1.75 eV vs. NHE) [33] was less positive than that of H₂O/O·OH pair (+1.99 eV vs. NHE). The migrated e⁻/h⁺ did not possess sufficient potential to produce ·O₂⁻ and ·OH, which was inconsistent with the ESR test results. Therefore, we reasonably proposed a Z-scheme (b) charge transfer mechanism. The potential of O₂/·O₂ pair was less negative than the CB of CdS (–0.65 vs. NHE) and more negative than the CB of TiO₂, so the photogenerated electrons transferred to the CB of TiO₂; then the photogenerated holes transferred to the VB of CdS, resulting in the accumulation of photogenerated electrons on the CB of TiO₂ and holes on the VB of CdS. The well-matched band structures of CdS and TiO₂ favor the photogenerated charge separation, which improves the charge transfer efficiency and inhibits recombination of charge carriers.
electrons on the CB of CdS would probably react with O$_2$ to produce O$_2^\cdot$. Similarly, the potential of H$_2$O/⋅OH pair was less positive than that of VB of TiO$_2$ (+2.91 vs. NHE) and was more positive than that of VB of CdS, so the retained holes on VB of TiO$_2$ would react with H$_2$O to produce ⋅OH. Due to the good electrical conductivity of Au NPs, the electrons generated from CB of TiO$_2$ could transfer to the VB of CdS more easily via the shuttle mediator. Consequently, the possible electrons transfer pathway in FSTCA is obtained in Fig. 4C (c). In detail, electrons generate on the CB of TiO$_2$ and CdS, and holes generate on their VB after light irradiation. Then, the electrons in the CB of TiO$_2$ transfer quickly through Au NPs to the VB of CdS and recombine with the holes, resulting in the formation of electrons in the CB of CdS and holes in the VB of TiO$_2$. Subsequently, strong oxidizing holes and strong reducing electrons react with O$_2$ and H$_2$O to form O$_2^\cdot$ and OH, respectively. Then, O$_2^\cdot$, OH, and h$^+$ reacted with ascorbic acid (AA) to form AA$^+$. Based on the above results, the possible mechanisms are as follows:

\[
\begin{align*}
\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{TiO}_2@\text{CdS}/\text{Au} + h^+ &\rightarrow e^- + h^+ \quad (1) \\
\text{O}_2 + e^- &\rightarrow \text{O}_2^\cdot \quad (2) \\
\text{H}_2\text{O} + h^+ &\rightarrow \text{OH} \quad (3) \\
\text{O}_2^\cdot/\cdot\text{OH}/h^+ + \text{AA} &\rightarrow \text{AA}^+ \quad (4)
\end{align*}
\]

3.3. Characterization of PEC immunosensor

The PEC immunosensor was fabricated under the optimal conditions (Supplementary material) for SARS-CoV-2N protein detection. The electrochemical impedance spectroscopy (EIS) was used to prove the layer-by-layer assembly of PEC immunosensor. Generally, the diameter of the high frequency of the semicircle of EIS was related to the electron transfer resistance ($R_{et}$). The larger the semicircle diameter is, the larger $R_{et}$ of the GCE/FSTCA electrode (Fig. 5A). The EIS exhibits a relatively smaller semicircle (curve a), indicating GCE/FSTCA has smaller $R_{et}$. After the step-by-step assembly of Ab$_1$, BSA, SARS-CoV-2N protein, and SiO$_2$@Au-Ab$_2$, $R_{et}$ gradually increased, indicating the immunosensor had been fabricated successfully.

Fig. 5B shows the photocurrent of the immunoconjugates at each stage. After the gradual modification of BSA, Ab$_1$, SARS-CoV-2N protein, and SiO$_2$@Au-Ab$_2$, the photocurrent decreased gradually. This may be attributed to the fact that large and insulated immune complexes...
weaken the light absorption and reduce the transfer of photogenerated electrons, which further proves the successful construction of the immunosensor.

3.4. PEC detection for SARS-CoV-2N protein

From the photocurrent curves (Fig. 5C, D), the photocurrent of the
system progressively decreased with the concentration of SARS-CoV-2 N protein increased from 10 pg mL\(^{-1}\) to 100 ng mL\(^{-1}\). In the SARS-CoV-2 N protein concentration range of 10 pg mL\(^{-1}\)–100 ng mL\(^{-1}\), the linear correlation equation is \(I (\times 0.1 \mu A) = 15.74 - 2.80 \log c\), with correlation coefficient of 0.983. Compared with the methods previously reported in Table S1, the proposed PEC immunosensor has a lower detection limit of 2.9 pg mL\(^{-1}\), which proves the successful construction of a sensitive PEC immunosensor for SARS-CoV-2 N protein detection.

### 3.5. Stability, selectivity and reproducibility

After the photocurrent was measured at ten on/off irradiation cycles, the photocurrent almost remained constant (Fig. 5E), demonstrating favorable stability. With Middle East respiratory syndrome coronavirus (MERS) N protein, influenza A (FluA) N protein, influenza B (FluB) hemagglutinin, Respiratory syncytial virus (RSV) attachment protein, G and bovine serum albumin (BSA), as the interfering substances (10 ng mL\(^{-1}\)), the selectivity of PEC immunosensor was measured. The PEC responses toward SARS-CoV-2 N protein (1 ng mL\(^{-1}\)) and its interferents was measured followed the above procedure (Section 2.2). The PEC responses of the interferents were similar to that of the blank, which was significantly different from the target detection, indicating that the PEC immunosensor possessed good selectivity (Fig. 5F). Five groups of parallel experiments were carried out on the target detection (1 ng mL\(^{-1}\)), and the photocurrent were 15.52, 15.23, 15.84, 15.56, 14.68 \(\times 0.1 \mu A\), respectively. The calculated relative standard deviation (RSD) was 2.86 %, showing good reproducibility of the PEC immunosensor.

### 3.6. Simulated simple analysis

The artificial saliva was purchased. The samples were prepared by adding 50, 500, and 2500 ng mL\(^{-1}\) of SARS-CoV-2 N protein (20 \(\mu L\)) into artificial saliva (1.0 mL). First, the prepared spiked real samples with various concentrations (500 \(\mu L\)) was added into the FSTCA/Ab precipitation (500 \(\mu L\)) and then reacted at 37 °C for 1 h. After the conjugates were washed by magnetic separation, SiO\(_2@\)Au-Ab (500 \(\mu L\)) was added for reaction at 37 °C for 1 h. Then, the immunocomplex was washed and dispersed in 500 \(\mu L\) of PBS. Finally, 15 \(\mu L\) of suspension were dried on the surface of ITO electrode for photocurrent test. As described in Table S2, the RSD varied from 2.1 % to 4.6 % and the recoveries were in the range 108.9–117.2 %. The fabricated PEC immunosensor has high specificity for detecting SARS-CoV-2 N protein.

### 4. Conclusion

In summary, an exquisite signal-off PEC immunosensor was designed for ultrasensitive SARS-CoV-2 N protein determination relying upon magnetic all-solid-state Z-scheme heterojunction FSTCA as photoelectric matrix beacon and SiO\(_2@Au\) as a signal quencher. FSTCA possessed excellent magnetic response can simplify the separation and washing process, while allowing immune recognition to be performed in the liquid phase. ESR spectra were used to identify the active intermediates and infer the possible photogenerated e\(^-\)/h\(^+\) transfer channel of FSTCA. The PEC immunosensor exhibited a wide linear range and a low limit of detection, providing an applicable method for the diagnosis of SARS-CoV-2 and an excellent strategy of PEC immunosensor.

CRediT authorship contribution statement

Aijiao Guo: Methodology, Writing, Writing- Reviewing and Editing. Fubin Pei: Visualization, Investigation, Data Curation. Shasha Feng: Data curation, Writing - Original draft preparation. Wei Hu: Investigation, Conceptualization. Pengjie Zhang: Formal Analysis, Investigation. Xihui Mu: Supervision, Resources, Data curation. Zhaoyang Tong:...
Declaration of Competing Interest

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.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.snb.2022.132800.

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