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# Cleaning strategy for carbon-based electrodes: Long-term propofol monitoring in human serum

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ABSTRACT

In this work, we present a novel electrochemical cleaning procedure for long-term electrochemical monitoring of propofol by using *boron-doped diamond* (BDD) and *pencil graphite electrode* (PGE). Propofol is an anesthetic that is widely used for long-lasting medical operations. Therefore, it is of great importance to be able to develop a sensor for long-term detection of propofol in the therapeutic range. Up to now, this aim could not be achieved due to loss of sensor sensitivity caused by the fouling phenomenon from propofol oxidation mechanism. We have developed intermittent cleaning steps to be able to ensure sensitive detection of propofol for more than 4 h. In addition to long-term monitoring, we also managed to detect the drug inside human serum by using PGE for *differential pulse voltammetry* (DPV) measurements achieving a *limit of detection* (LOD) of $0.82 \pm 0.08$ μM, which is even lower that the physiological concentration usually used range of propofol ([1–60] μM).

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## 1. Introduction

*Propofol* (2,6-diisopropylphenol) is a very well-known intravenous anesthetic drug widely used in surgical operations and in critical care settings. Its large popularity stems from its favorable properties: a short duration of action and a consequent rapid recovery [1]. In order to obtain a suitable *depth of anesthesia* (DOA) of the patient, an effective and appropriate concentration of propofol, which ranges among 0.25–10 μg/L (1–60 μM), is injected in the patient's veins. The infusion rate is chosen depending on patient's physical characteristics (e.g. age, sex, weight, etc.) and on the type of surgical operation [2]. To this purpose, *target controlled infusion* (TCI) pumps are largely adopted to drive the anesthetic infusion to achieve and maintain a specific target concentration [3]. Mathematical models are implemented on the TCI to statistically predict the plasma drug concentration in the patient to balance the dosage accordingly [4]. Nevertheless, these mathematical models are not able to reproduce the inter-patient variability in terms of drug metabolism and tolerance [5]. All in all, this variability among patients and clinical conditions may affect the efficiency of the infusion process leading to over- or under-dosages [6]. To overcome these limitations and to avoid risk of wrong dosage, a continuous *therapeutic drug monitoring* (TDM) [7] system has to be integrated with the TCI to keep the concentration levels of drugs under control during anesthesia.

Up to now, various technologies have been developed to determine the propofol concentration in human body fluids. Most of the studies are focused on chromatographic techniques based on *high performance liquid chromatography* (HPLC) [8], and *chromatography-tandem mass spectrometer* (C-MS) [9]. Although their high sensitivity, this techniques are based on bulky instrumentation difficult to be integrated in portable systems. In addition to these techniques, detection of propofol by breath analysis has been proposed [10,11], but the correlation between blood and breath propofol concentrations is still not clear. For this reason, serum samples are preferred as convenient media for propofol concentration monitoring [12].

A common surgical operation normally lasts for up to several hours (~4 h), therefore a system for propofol monitoring should ensure a reliable and accurate response over this period of time. Electrochemical sensors are good candidates for drug monitoring [13] and they have been already investigated for propofol [14–16]. From these studies it emerges that propofol, that is a phenolic compound, can be easily oxidized and sensed electrochemically, but free radicals produced by phenolic oxidation result

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in electro-polymerization. This reaction causes electrode fouling that decreases the sensor sensitivity upon subsequent measurements [17,18].

To address this undesirable phenomenon, in a recent study, a polymeric membrane-coated electrochemical sensor has been developed [14]. It is capable of detecting propofol inside serum-like media with a detection limit of 0.012 ± 0.004 μM. The proposed electrode is highly promising in terms of detection limit and resistance to fouling, but the deposition of the membrane on the electrode surface is a critical step to obtain a proper thickness and uniformity, and, moreover, the major problem of PVC membrane sensors is their low physical and mechanical resistance for long-term usage [19]. However, difficulties in the fabrication process makes the reproducibility of the electrodes uncertain and this may result in over- or under-estimation of the propofol concentration in patient's plasma. More recent studies have reported propofol detection by adopting *molecular imprinted polymer* (MIP) biosensors [20]. Although there has been promising results, the possibility of having heterogeneous pore size distribution might result in sluggish mass transport which is not appropriate for long-term monitoring during surgery [21].

Therefore, in this work we have validated a ready-to-use and robust point-of-care sensor for long-term monitoring of propofol to be adopted during anesthesia practices. BDD electrodes and PGEs were tested in terms of change in their sensitivity and surface characteristics upon long-term monitoring. Moreover, the effect of these two electrode materials on propofol electro-oxidation and fouling was widely analyzed to fully understand the reaction mechanism.

We have proved that BDD is more resistant to fouling and deactivation of the surface with respect to PGE, thanks to the lower adsorption capabilities [22]. This is due to the fact that undoped diamond is normally electrically insulating because of its large bandgap, but it is made conducting by doping it with boron [23,24]. On the other hand, PGEs exhibit a better sensitivity. Two surface cleaning methods: in *phosphate buffer saline* (PBS) and in sodium hydroxide (NaOH) have been developed. Thanks to optimized electrochemical cleaning procedure introduced after the sixth measurement of propofol, a sensitive and reproducible detection for 4 h has been successfully achieved. Finally, experimental results with PGE show that the detection of propofol is possible even in presence of interfering compounds, e.g. *p-acetamidophenol* (APAP).

## 2. Experimental section

### 2.1. Chemicals

2,6-Diisopropylphenol (propofol) was purchased from TCI chemical and dissolved in 0.1 M NaOH to prepare the stock solution of 5.4 mM. Subsequent dilutions of propofol stock solution were done inside PBS (10 mM, pH 7.4) or serum to obtain concentra-

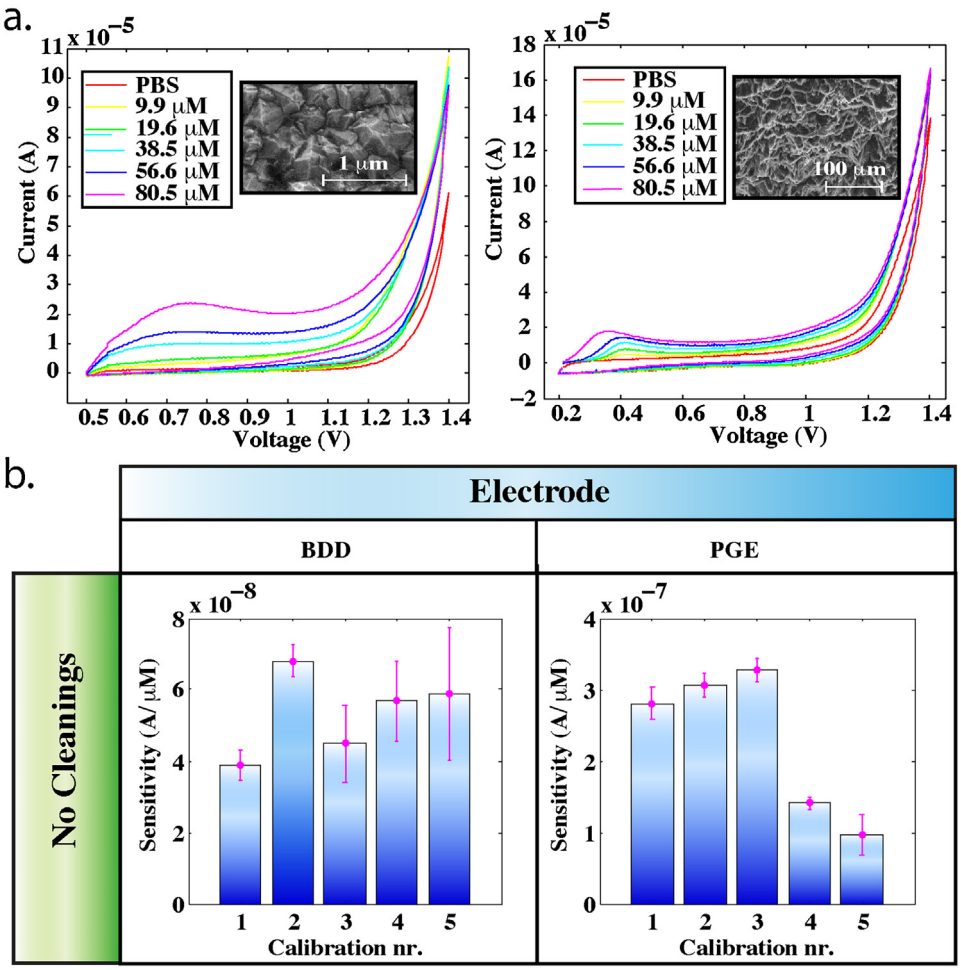


**Fig. 1.** a) Typical CV of propofol with PGE and BDD for various propofol concentrations [9.9–80.5] μM. (b) Change in sensitivity of BDD and PGE with respect to different number of calibrations performed consecutively in PBS (pH:7.4). Error bars represent the standard deviation from the linear regression analysis performed for *S* evaluation ($n = 5$, points in each calibration).

tions of: [9.9 – 19.6 – 38.5 – 56.6 – 80.5] μM. The compounds APAP, $KH_2PO_4$, $K_2HPO_4$, NaOH, $KNO_3$ and heat inactivated human male serum were purchased from Sigma Aldrich.

### 2.2. Instrumentation and procedures

#### 2.2.1. Electrochemical analysis

Rotating disk BDD/*silica substrate* (Si) *working electrode* (WE)s (electro active area of 12.4 $mm^2$, 700 ppm) were purchased from NeoCoat SA. Pencil mines with diameter of 0.5 mm were used as PGE WE and a commercial mechanical pencil was adopted as electrode's holder. The PGE was dipped for 8 mm into the solution in order to have an electro-active area ($A_{base} + A_{lateral} = (\pi \times (0.5/2)^2) + (2 \times \pi \times (0.5/2) \times 8) = 12.7\ mm^2$) comparable with the BDD electrode (12.4 $mm^2$). The good electrical contact was obtained by soldering the metallic parts of pencil with a copper wire. The Ag|AgCl|3.0 M KCl *reference electrode* (RE) was provided by Metrohm and a Pt wire was used as *counter electrode* (CE). *cyclic voltammetry* (CV)s and DPVs were performed with a Metrohm Autolab system (PGSTAT 302N) in conjunction with Nova 1.11 software. Data analysis and plotting was done in Matlab R2013a and Excel 2011.

In particular, for propofol detection, the peak height was evaluated with a Matlab script respect to a constant baseline. The constant baseline has been set for each calibration as average value of the ordinates of the points in the area before the peak (steady state).

For interference study, to better identify and separate the contribution of the two target compounds (APAP and propofol), a Gaussian decomposition of the CV curve was executed in Excel by using the integrated Solver tool. CV measurements were conducted by using PGE and BDD in the range from +0.2 V to +1.4 V and from +0.75 V to +1.4 V, respectively, at a scan-rate of 0.1 V/s. Typical CV scans are reported in Fig. 1a. Propofol gives an oxidation peak used for evaluation. CV plots report the area of the peak. DPV measurements were performed with PGE in the potential range of [0.0 to +1.1] V with interval time of 0.2 s, modulation amplitude of 50 mV, modulation time of 50 ms and scan-rate of 0.025 V/s. Prior to measurements with BDD, a preliminary conditioning inside 0.1 M $KNO_3$ solution at +2.2 V for 900 s was done for an activation of the electrode surface, as indicated by the Supplier.

Electrochemical characterization of BDD and PGE electrodes was done via CV technique for the evaluation of sensitivity and LOD values over five subsequent set of 5-points-calibration experiments. Sensitivity ($S$) was calculated as the slope of the calibration curve (peak current versus concentration) while LOD was calculated as $LOD = 3 \cdot \frac{(SD)_{blank}}{S}$, where $(SD)_{blank}$ is the standard deviation at blank measurements ($n = 3$). Furthermore, LOD was experimentally determined in serum by performing DPVs at null and at 0.85 μM propofol concentration and by registering an increase of the blank signal when propofol is injected.

#### 2.2.2. Cleaning procedures

Two cleaning procedures were tested for eliminating the effects of fouling caused by propofol oxidation. The electrochemical cleaning was performed after every six CV measurements.

- NaOH cleaning was done inside 10 ml of 0.1 M NaOH solution by carrying out 10 cycles of CVs in the same potential range where the drug was sensed ([+0.75 to +1.4] V for BDD and [+0.2 to +1.4] V for PGE).
- PBS cleaning consists of a *chrono amperometry* (CA) performed by applying +1.4 V for 30 s without stirring the solution to that the cleaning *per se* is sufficient. We have used 10 ml of 10 mM PBS (pH 7.4).

For the optimization of cleaning procedures different combinations of parameters have been investigated. For NaOH cleaning the effect of number of scan (2, 5 and 10) has been tested while for PBS cleaning various applied fixed potentials (+1, +1.2 and +1.4 V) has been investigated for a constant duration (30 s). Results from this optimization study for PGE and BDD are in Supporting Information (Figs. 1 and 2, respectively).

#### 2.2.3. Surface characterization

The surface characterization of the electrodes was performed by using an XLF30-FEG *scanning electrode microscopy* (SEM) instrumentation in the *Interdisciplinary Center for Electron Microscopy* (CIME) at EPFL. It has a 1–30 kV Schottky field emission gun and a *secondary electrons* (SE) imaging resolution of 2 nm at 30 kV; 8 nm at 1 kV. The samples have been inserted into the SEM vacuum chamber in dry conditions. The SE images were taken by applying an accelerating voltage of 20 kV and a resolution of 200 μm.

## 3. Results and discussion

The experiments performed to design an electrochemical sensor for long-term propofol monitoring in serum, could be sub-grouped into two: (i) characterization of various electrode materials in terms of electrochemical and surface characterization techniques to check if the LOD and sensitivity ($S$) are affected by the time course and detection media and (ii) electrochemical detection of propofol inside human serum.

### 3.1. Electrode fouling phenomenon

Electro-oxidation of propofol causes free radicals that electropolymerizes on the electrode surface forming a passivating layer that prevents the long-term stability of the sensor [15]. The sensitivity values for PGE and BDD electrodes over five calibration curves (five points each) are shown in Fig. 1b. It is evident that both the electrode materials are affected by the fouling effect, but it is more evident in PGE measurements. The PGE reaches higher sensitivity values ($((2.3 \pm 1.0) \times 10^{-07}$ A/μM) respect to the BDD electrode ($((5.3 \pm 1.2) \times 10^{-8}$ A/μM), but there is a sharp sensitivity decrease after the third calibration. On the other side, the BDD obtains similar sensitivities in all the consecutive calibrations, but there is a high variability of these results limiting the reproducibility. To further underline this phenomenon subsequent calibration lines are reported in the *Supporting Information*, Figs. 3 and 4. To avoid the formation of the passivating layer and to stabilize the sensitivity values in time two cleaning procedures has been designed and validated. Furthermore, the electrode-fouling phenomenon was further investigated through SEM surface characterization and electrochemical studies by analyzing scan-rate and pH dependencies.

### 3.2. Surface characterization of the fouling layer

SEM analysis was done to observe the effects of fouling due to a calibration set of experiments (five concentration values) and cleaning on PGE and BDD electrodes. Surface images of the BDD electrode have not shown any evident of fouling, not shown here. On the other hand, Fig. 2 shows SEM images of bare PGE, after one calibration set of experiments (five concentration values), after NaOH cleaning and PBS cleaning. Fig. 2a shows that bare PGE is characterized by graphite striae on the lateral surface and small pointed tips at the base after CVs in PBS electrolyte solution. On the contrary, after a propofol calibration, a deposit layer is clearly seen on both lateral and base surface of the electrode (Fig. 2b). This passivating layer of propofol fouling covers the superficial structures of the electrode and causes the decrease of sensitivity as it is

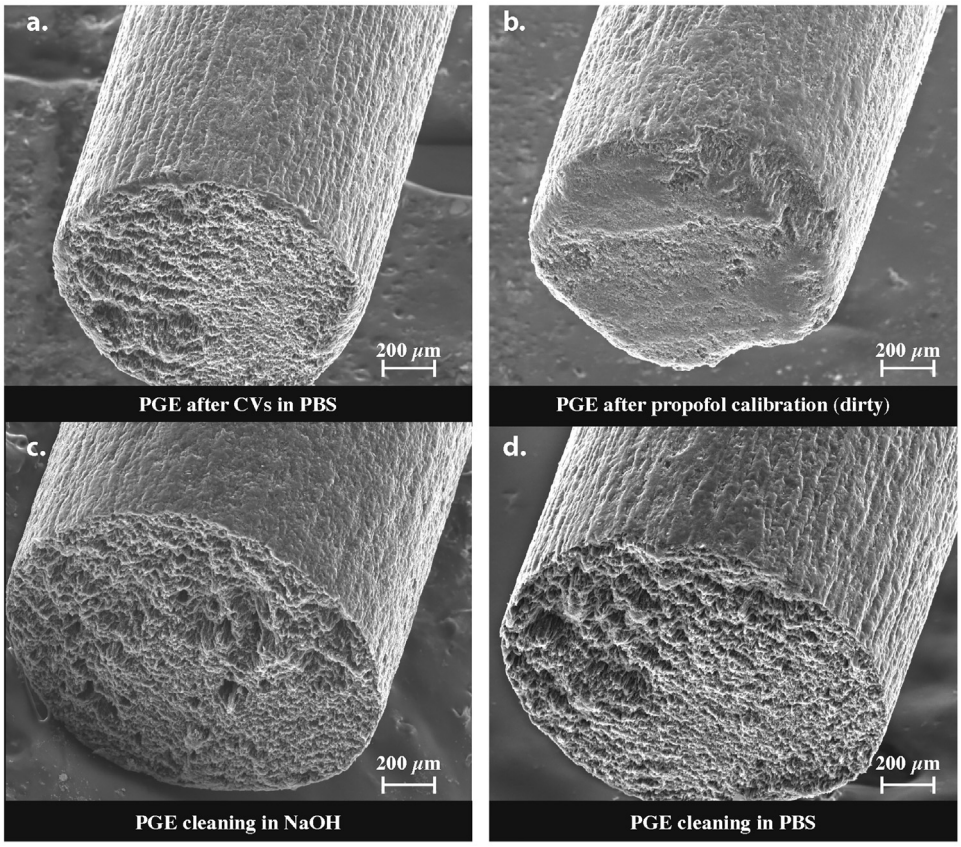


**Fig. 2.** SEM images: (a) bare electrode after 5 cycles of CV in only PBS (background electrolyte), (b) after one propofol calibration, (c) after NaOH cleaning and (d) after PBS cleaning.

shown by electrochemical characterization results. After performing cleaning procedures (NaOH cleaning Fig. 2c and PBS cleaning Fig. 2d) this layer is removed and the morphology of the PGE is recovered back to its original bare structure.

To support SEM images CVs in 5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ has been performed before and after cleaning in order to compare the electro-active surface area [25] (*Supporting Information*, Fig. 5). The electrochemical active surface areas of the electrode has been evaluated from Randles–Sevick equation as follow: $A = i_p/(286.6 \times n^{(3/2)} \times D^{(1/2)} \times C \times \nu^{(1/2)})$, where $i_p$ is the anodic peak currents from CV data, $D$ is the diffusion coefficient ($cm^2/s$), $C$ is the concentration of the electro-active species in the bulk solution ($mol/cm^3$), and $\nu$ is the scan-rate (V/s). The ferro/ferricyanide peaks decrease after propofol calibration with 5 concentrations. That shows the effect of propofol polymerization on the active area of the electrode. After PBS and NaOH cleaning the peaks are recovered again, because of the fact that the cleaning procedures are effectively regenerating the surface of the electrode. According to the results before and after cleanings, it is concluded that the active area is recovered of 99.6% and 71.2% for PBS and NaOH cleaning, respectively.

### 3.3. Electrochemical analysis of the fouling layer

The electrochemical formation of the fouling layer was analyzed in order to better characterize the mechanism of propofol electro-oxidation. Therefore, in this section the effects of pH and scan-rate are investigated

By studying the effect of pH on propofol electro-oxidation the number of electrons exchanged in the reaction are evaluated. Two cycles of CV were performed in 30 μM propofol solution at different pH solutions in the range of 2–10. As it is evident from Fig. 3a, the pH of the solution influences the peak current and the peak potential in a considerable extent. In particular, although there is not a trend for peak current, it is clear that the peak potential shifts to more negative values for higher pH values. Plot of the anodic peak ($E_{pA}$) potential versus pH exhibits a slope value equal to 62 mV (Fig. 3b) that is close to 59 mV predicted by the Nernst equation for process involving equal number of protons and electrons [26]. This result demonstrates that propofol electro-oxidation involves the exchange of one proton and one electron [27]. In addition to pH, the effect of the scan-rate was also investigated by performing CVs in 30 μM propofol solution ([0.025, 0.05, 0.1, 0.15, 0.2] *V/s*). By plotting the peak current versus the square root of scan-rate, a non-linear trend is obtained, as shown in Fig. 3c. Similar trend has been obtained also for the scan-rate dependency (not reported). This proves that the reaction is not a diffusion-controlled process, because of characterized by a combination of adsorption and fouling phenomenon at the electrode's surface.

We have already reported the results from $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (5 mM) CV analysis in Fig. 5 that emphasis the fouling effect. Indeed, both the oxidation and reduction peaks current of $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution decrease in subsequent CV measurements, indication of the formation of a passivating layer on the electrode surface as a result of propofol subsequent calibrations [28]. According to these results and previously suggested works [29], chemical oxidation of propofol is illustrated in Fig. 3e. When the positive potential is applied, propofol is oxidized by one electron and one proton removal and three types of intermediate radicals would possibly form and initiate the polymerization process that results in electrode fouling (dashed line). Scan-rate analysis was also performed at BDD electrode

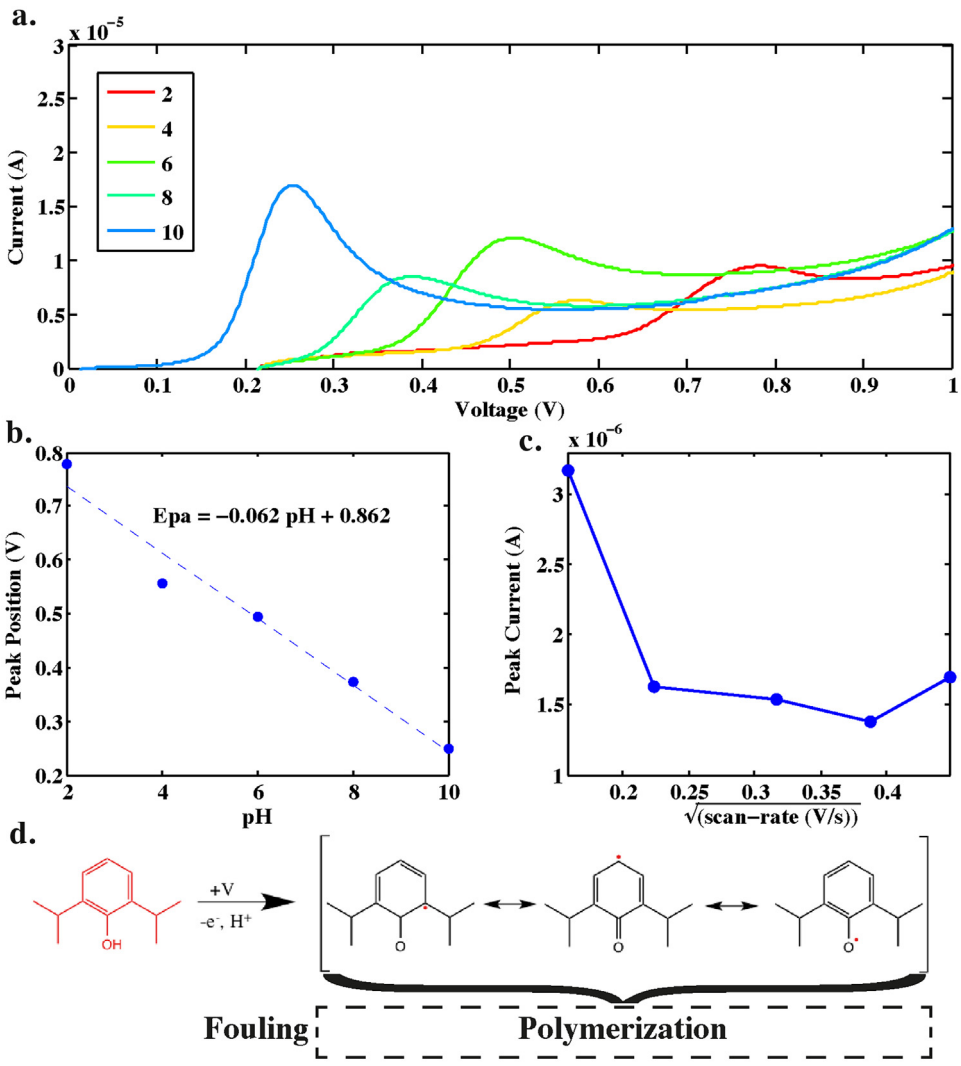


**Fig. 3.** pH and scan-rate studies of 30 μM propofol electro-oxidation at PGE: (a) CVs in solutions at different pH [2–10], (b) linear dependency between peak position and pH variation, (c) peak current amplitude VS square root of scan-rate, and (d) suggested mechanism of propofol electro-oxidation reaction.

([0.05, 0.1, 0.15, 0.2] *V/s*). Similarly, also the propofol oxidation at BDD electrode is not a diffusion-control process (*Supporting Information*, Fig. 6).

### 3.4. The cleaning of the fouling layer

In order to provide a long-term monitoring of propofol, electrochemical cleanings of BDD and PGE electrodes were tested and validated. Fig. 4 shows the results of sensitivity for BDD and PGE electrodes over each calibration curves (up to five) with cleaning procedures; i.e. PBS or NaOH cleaning, applied in between two subsequent calibration curves. It is clear from Fig. 4 that, even if both PBS and NaOH cleanings have an improvement against the fouling phenomenon, which was affecting both the electrodes' calibrations without intermediate cleaning (shown in Fig. 1b), NaOH guarantees the best maintenance of the electrode over time. In particular, the sensitivity values after NaOH cleaning are higher and characterized by the lowest variability compared to the use without cleaning or after cleaning in PBS.

From Fig. 4 it is possible to conclude that, even if BDD electrode sensitivity values are more stable, especially if applying NaOH cleaning step, PGE is more sensitive to propofol. Therefore, by adopting a proper cleaning procedure, its high sensitivity is favorable for direct detection in human serum. Five calibrations (five concentrations per each) were carried out resulting in 25 subsequent measurements adding up to four hours of total measurement time. From these results, therefore, long-term monitoring is enabled for more than four hours. According to diagnostic definition, which is [30], we have achieved a continuous monitoring system by measuring one sample every 10 min (6 measurements for one hour). However, by combining cleaning and measuring procedure, we have evaluated that the system provides a sample measurement every minute that is even better in the case of drugs with fast clearance as propofol.

The measurements in time for the best electrode-cleaning combinations are shown in Fig. 5; i.e. BDD with NaOH cleaning and PGE with PBS cleaning.

If a final application in anesthesia delivery and long-term monitoring is considered, it could be more convenient to avoid extra chemicals and instead using PBS for cleaning. Adding NaOH as a cleaning solution would complicate the system design and require extra time whenever cleaning is needed. Indeed, considering the final application, we also tested the cleaning in PBS with still 80 μM propofol concentration inside and comparable results with only PBS solution are obtained (see Fig. 7 in *Supporting Information*). Therefore, the cleaning is successful also in presence of the analyte itself.

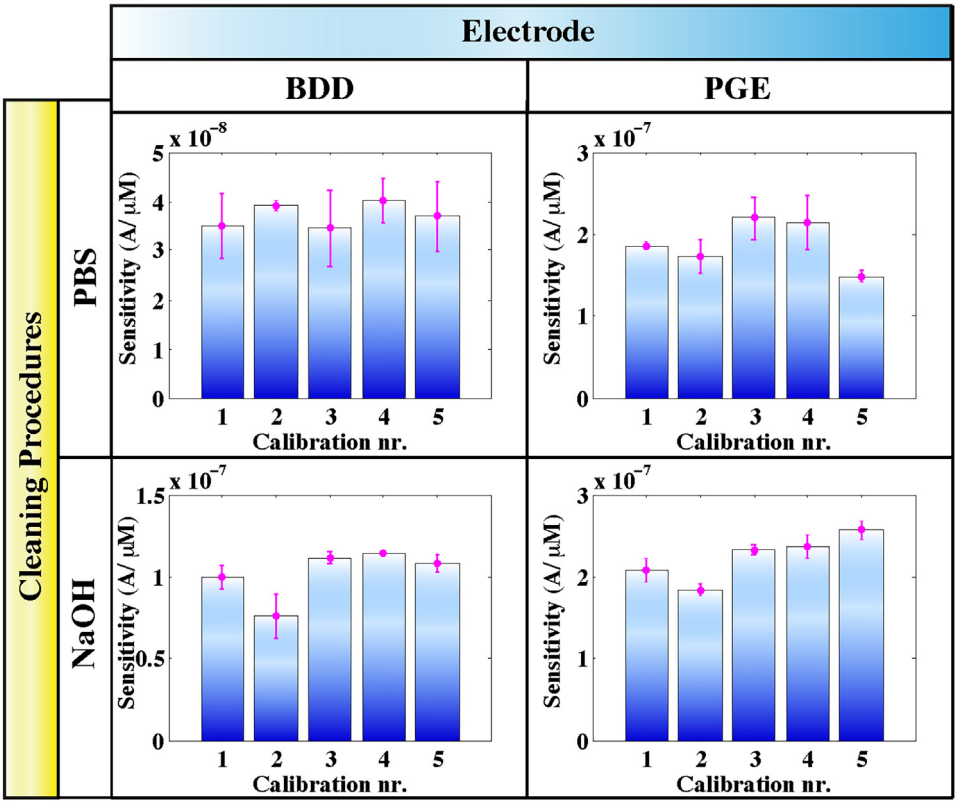


**Fig. 4.** Change in sensitivity ($S$) of PGE and BDD with respect to number of calibration and type of intermediate cleanings with PBS and NaOH. Error bars are evaluated as one standard deviation from the linear regression analysis for $S$ evaluation ($n = 5$, points each calibration).

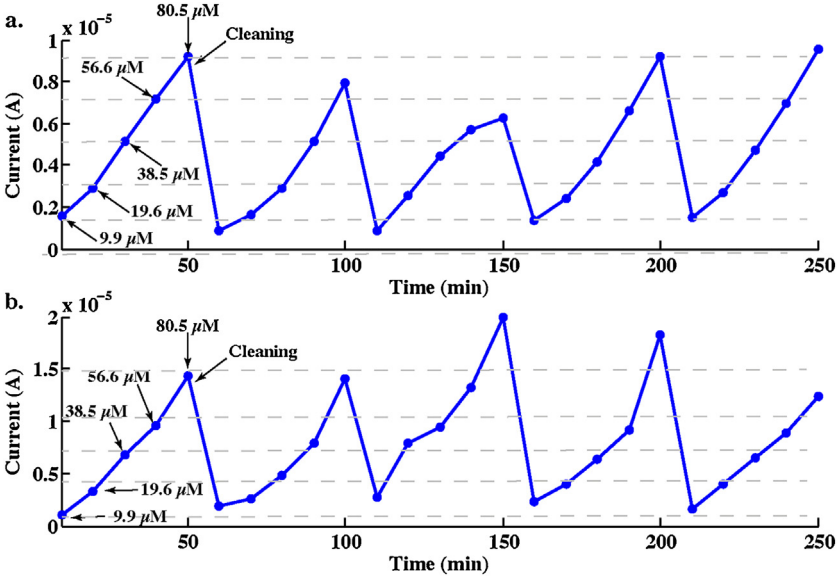


**Fig. 5.** Long-term electrochemical propofol monitoring with intermediate cleaning step after the detection of highest concentration (80.5 μM); current response over time (a) BDD electrode with NaOH cleaning and (b) PGE with PBS cleaning. The arrows indicates the points where the propofol concentration was changed and where cleaning procedure was implemented. Successive cycles have the same trend in concentration as the one in first cycle.

Finally, the LOD evaluated for PGE with PBS cleaning and BDD with NaOH cleaning are $3.14 \pm 1.13$ μM and $2.49 \pm 0.90$ μM, respectively, both are in the physiological range.

### 3.5. Interference study

Interferences between APAP and Propofol oxidation processes have been evaluated with PGE in PBS background electrolyte. Indeed, APAP is an antipyretic, non-opioid analgesic worldwide adopted. It can be administered by intravenous route in hospital settings to critically ill and surgical patients [31]. Therefore, it is normally present in patient's blood when propofol is infused. Other interfering compounds, i.e. ascorbic acid, cysteine, uric acid, were not investigated since their oxidative peaks are not in the same potential window of propofol. Indeed, ascorbic acid and uric acid oxidation peaks shown to be at +0.1 V and +0.5 V, respec-

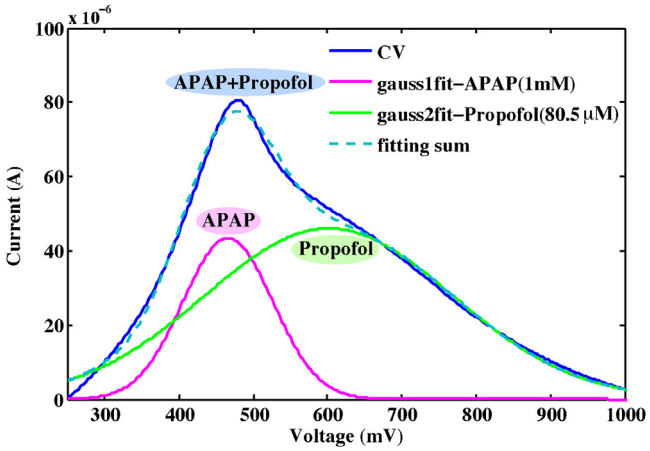


**Fig. 6.** APAP interference study: Gaussian decomposition of the cyclic voltammogram (CV procedure ([+0.2 to +1.4] V, scan-rate 0.1 V/s at PGE) belongs to the mixture of APAP (1 mM) and propofol (80.5 μM).

tively (at graphite-based WE and saturated calomel electrode as RE) [32]. Moreover, cysteine had an oxidation peak at 0 V on modified graphite electrodes (saturated calomel electrode as RE) since the sensitivity of bare electrodes were very low [33].

On the other hand, APAP is an electro-active phenol compound as propofol and its oxidation CV peak appears at around 500 mV for clay-modified carbon paste electrodes [34].

Fig. 6 shows a resulting oxidation peak for a solution containing 1 mM APAP and 80.5 μM propofol with background correction. This isolated current peak region was fitted by two Gaussian functions centered at 466 mV and 601 mV. Since the two Gaussian components are well detectable, it is possible to identify and separate the contribution of paracetamol (*gaussian1fit* at 466 mV) from the current peak in the voltammogram (*gaussian2fit* at 601 mV).

After the optimization of the parameters related to cleaning and the pH and scan-rate studies, the detection of propofol inside human serum was achieved in order to provide a system able to be adopted in anesthesia delivery practices. A successful detection of propofol has been done with DPV technique by using PGEs. DPV has been introduced and preferred to CV since it is more sensitive technique [35], therefore more suitable for serum measurements. This technique can be performed in time by introducing cleaning procedures as described in the manuscript for CVs. First, calibrations of propofol were carried out by DPV in PBS to identify the oxidation peak position and the best potential range, Fig. 7a. Then, the same set of calibrations was carried out in full serum. Fig. 7b shows a visible oxidation peak in the same potential range within PBS. The peak current values increases linearly with increasing propofol concentrations that has a linear calibration equation with an $R^2$ of 0.99 ($n = 3$). By comparing the current values (and accordingly the sensitivities) of PBS and serum results, we can see that PBS values are higher than in serum. This is due to the fact that propofol is highly lipophilic drug and more than 95% bound to human serum components, in particular to albumin [36]. Therefore, only a small fraction (called *free drug concentration*) is able to be detected electrochemically. Furthermore, serum is a complex solution rich in components which also affect the electrode performance by reducing the sensitivity. However, from the obtained calibration curve, the LOD was calculated to be 0.82 μM with 9.3% *relative standard deviation* (RSD) and this concentration is in the physiological range ([1–60] μM).

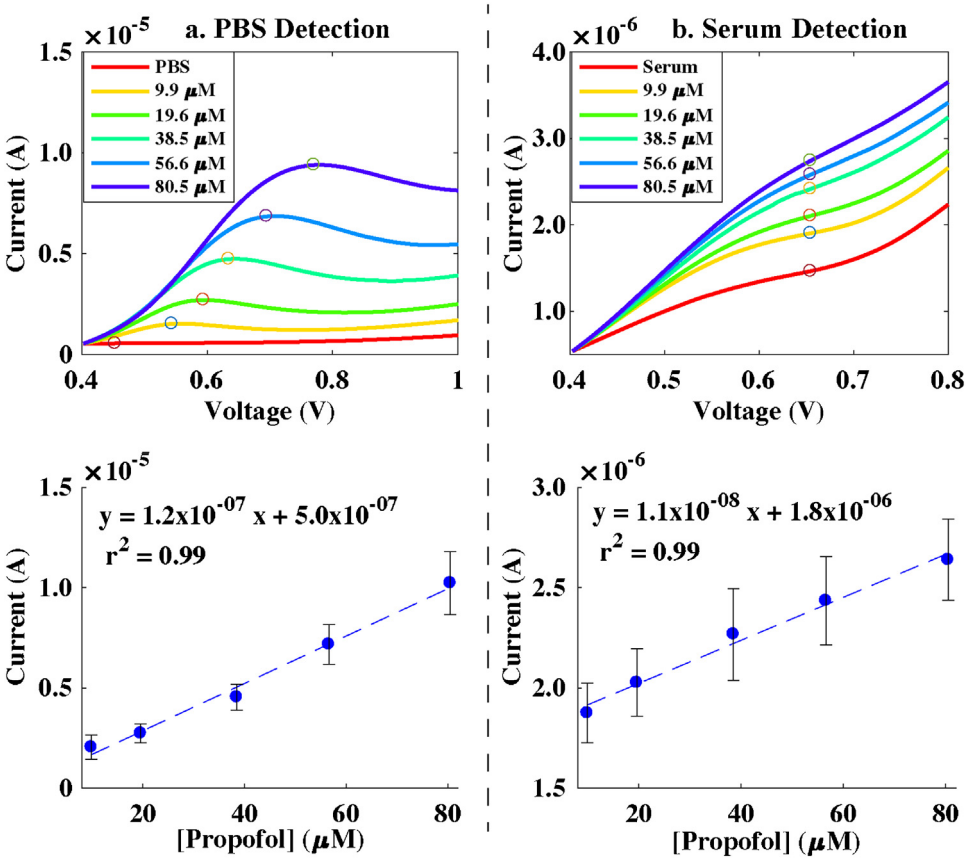


**Fig. 7.** DPV voltammograms and calibration lines for various concentrations of propofol detection by PGE based on DPV method (a) in PBS and (b) in serum for the experimental procedures detailed in Section 2.2, for $n = 3$.

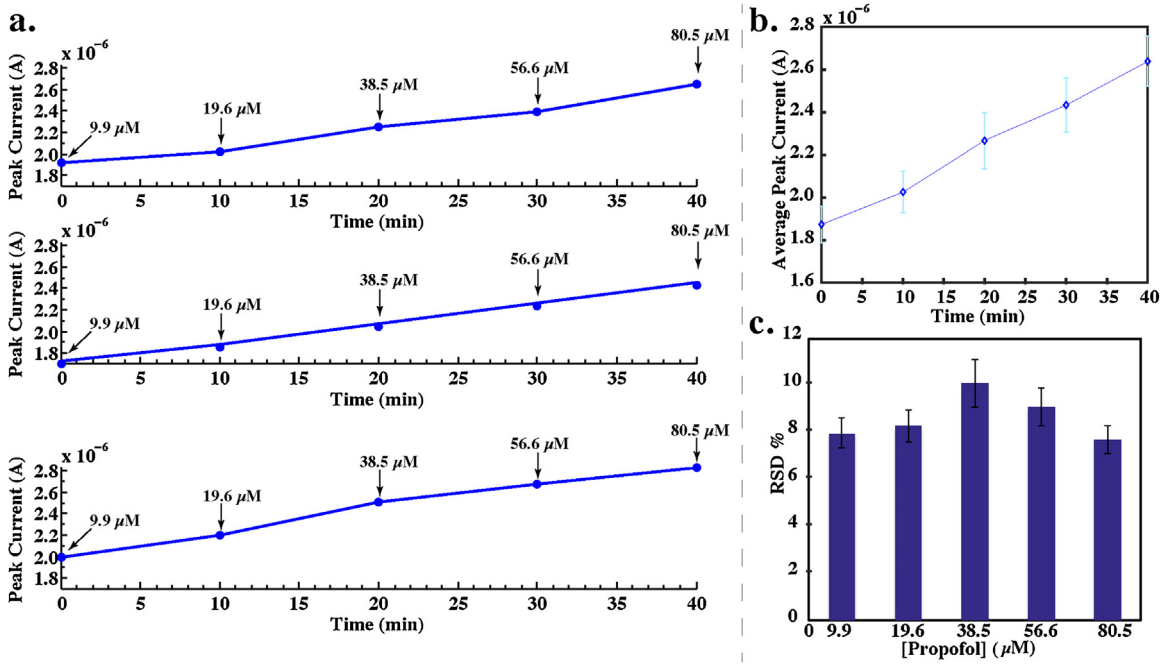


**Fig. 8.** Reproducibility of PGE: (a) propofol oxidation peak trend in time of three different PGE sensors running DPV procedure at various concentrations (9.9 – 19.6 – 38.5 – 56.6 – 80.5) μM, (b) change in oxidation peak current by time and (c) bar graph of RSD% (<15%) with error bar evaluated according to error propagation analysis [38].

**Table 1**
Comparison of the performance of the sensors for propofol sensing presented in literature: ready to use (*RtU*), electrochemical technique (*T*), LOD (error limits are evaluated as standard deviation of the dataset $n = 5$), long-term monitoring (*LTM*), possibility to detect in human serum background electrolyte (*HS*) and on-line electrochemical cleaning procedures implemented (*CPI*) in which solution (*CS*) are taken in consideration.

| Ref. | WE | RtU | T | LOD (μM) | LTM | HS | CPI | CS |
|---|---|---|---|---|---|---|---|---|
| [16] | GC SPE | × | CV | 3.2 ± 0.1 | – | – | × | – |
| [14] | PVC WE | × | CV | 0.08 ± 0.05 | 3 h | – | × | – |
| | PVC WE | × | CA | 0.012 ± 0.004 | – | √ | × | – |
| This work | BDD | √ | CV | 2.38 ± 0.5 | >4 h | – | √ | PBS |
| | BDD | √ | CV | 2.4 ± 0.9 | >4 h | – | √ | NaOH |
| | PGE | √ | CV | 8.1 ± 5.6 | >4 h | – | √ | PBS |
| | PGE | √ | CV | 3.1 ± 1.1 | >4 h | – | √ | NaOH |
| | PGE | √ | DPV | 0.82 ± 0.08 | – | √ | – | – |

Fig. 8 compares the performance in time of three different PGE electrodes in propofol DPV monitoring. It is evident that the three obtained trends are very similar; hence proving the reproducibility of the results. Measurements reproducibility was further evaluated by estimating RSD% among measurements at the same propofol concentration, as shown in Fig. 8c. An average value of 8.6% RSD was obtained that is considered accepted for medical applications [37] and it reflects the precision among the three different tested electrodes. By comparing the obtained results with the literature, summarized in Table 1, we can conclude that both our sensors are suitable for reliable propofol detection. In this work, for the first time, on-line electrochemical cleaning procedures against fouling effect, have been proposed for the direct detection of propofol. NaOH cleaning solution results to obtain the lowest LOD. Finally, the lowest LOD was achieved in human serum by performing DPV technique with PGE, obtaining a sensitivity of 0.011 μA/μM. Main advantage of this technology is that it can be adopted as propofol sensors in an extremely easy- and ready-to-use procedure.

## 4. Conclusions

The objective of this work was the realization of a ready-to-use and robust point-of-care sensor for long-term monitoring of propofol. Therefore, we optimized and validated a novel intermittent cleaning strategy, including on-line cleaning, for sensing propofol over time (up to 4 h) by using BDD and PGE. The two kinds of electrode were tested and compared in terms of sensitivity in time by electrochemical analysis and by surface characterization through SEM imaging. Moreover, the effect of these two electrode materials on propofol electro-oxidation and fouling was widely analyzed to fully understand the chemical reaction mechanism (pH and scan-rate analysis).

The issue of fouling was successfully addressed by introducing optimized cleaning steps either in PBS or in sodium hydroxide (NaOH), enabling the long-term propofol monitoring, being able to measure the drug up to 4 hours. BDD electrodes provided lower sensitivity values compared to PGE. The sensitivity and reproducibility in long-term monitoring was evaluated through 25 CV measurements, corresponding to more than 4 h of acquisition time. We obtained LOD of 2.38 μM with 21% RSD, and LOD 3.14 with 36% RSD, for BDD and PGE, respectively.

Finally, we performed a direct detection of propofol in human serum by using PGE as WE, to exploit its higher sensitivity, and DPV as electrochemical technique, which is highly sensitive. The LOD was evaluated and experimentally verified as 0.82 μM with 9.3% RSD that is even lower the propofol physiological range ([1–60] μM).

Our future focus will be on investigation of unknown or mock samples for real-time settings as well as developing a feedback-controlled close-loop system for detection and delivery of propofol.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.snb.2018.04.082.

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