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Method Article

Microelectrodes from PEDOT-carbon nanofiber composite for high performance neural recording, stimulation and neurochemical sensing



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A B S T R A C T

This present method describes a versatile approach for the electrochemical synthesis of a composite material of Poly (3,4-ethylenedioxythiophene) (PEDOT) and Carbon Nanofibers (CNFs) for neural interfaces and biosensing applications. Oxidized CNFs were utilized as dopants of PEDOT to prepare the composite coating through electrochemical deposition on microelectrodes arrays (MEA). The experimental results of this study showed that PEDOT:CNF microelectrodes exhibit remarkable electrochemical properties, combining low impedance, high surface area, high charge injection capability and reliable neurotransmitters monitoring using amperometric techniques. Taken together, these results suggest the great potential of PEDOT:CNF composite for developing next-generation multifunctional microelectrodes for applications in neural therapies.

- A simple approach for the electrochemical synthesis of PEDOT:CNF composite material on microelectrodes for neural interfaces and neurochemical sensing.
- PEDOT:CNF microelectrodes exhibit remarkable electrochemical properties, combining low impedance and high charge injection capabilities.
- PEDOT:CNF microelectrodes allowed the reliable detection of neurotransmitters with improved sensitivity.

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A R T I C L E I N F O

Method name: Electrochemical synthesis of PEDOT:CNF composite on microelectrodes arrays

Keywords: PEDOT:CNF, Carbon nanofibers, Microelectrodes, Neural interfaces, Electrical stimulation, Electrochemical sensing

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Specifications Table

Subject Area:	Materials Science
More specific subject area:	Nanostructured materials Neural interfaces Electrochemical sensors
Method name:	Electrochemical synthesis of PEDOT:CNF composite on microelectrodes arrays
Name and reference of original method:	Carbon nanofiber-PEDOT composite films as novel microelectrode for neural interfaces and biosensing <i>Biosensors and Bioelectronics</i> , Volume 165, 2020, Pages 112413
Resource availability:	Not applicable

Method details

Background

Recent progress in the field of neural interfaces raises the need for novel multifunctional microelectrodes that are capable to meet the performance criteria of a number of neuronal interactions including neural recording, stimulation and sensing of bioactive molecules at the electrode-tissue interface. For neural recording, the microelectrode should have a low impedance across frequencies of interest for electrophysiological recordings (10 Hz–10 kHz) [1–4], while keeping a spatial footprint as small as possible to record the activity of small neuron population, down to the single cell [20]. This is beneficial to increasing the signal-to noise ratio (SNR) during *in vivo* neural recording. For electrical stimulation purpose, the electrode must display a high storage capability to safely inject millisecond current pulse with current range in the μA thus decreasing both electrode polarization and heat generation during neural stimulation [5].

In principle, the specific capacitance of an electrode may be greatly enhanced by introducing porous and high surface area organic materials into the electrode, thus compensating for a reduction of electrode size. Among the various organic materials reported in literature available to meet such requirements, conductive polymers such as Poly (3,4-ethylenedioxythiophene) (PEDOT) has a been popular choice that allow direct delivery of electrical, electrochemical and electromechanical signals at the electrode-tissue interface [1,6, 17]. PEDOT-coated electrodes have been considered for biomedical [18] and bioelectronic applications [2, 10, 11, 13] as well as in the fabrication of devices for neuronal interfaces [1, 7] and electrochemical sensing and actuating devices [8, 12, 16]. On the other hand, carbon nanomaterials have displayed a wide array of key properties and are also promising candidate for such applications. Charged carbonaceous nanomaterials such as carbon nanotubes CNTs or graphene oxide (GO) have been used (as dopant) in conjunction with PEDOT for the purpose of improving the electrochemical stability [9], charge storage delivery [6] and sensitivity of PEDOT electrodes for neurochemicals sensing [23]. These improvements come from both bulk and surface properties of these nanomaterials and their corresponding nanomaterials, including large surface-to-volume ratio and specific surface area, better electrocatalytic activity, and fast electron transfer kinetics compared to traditional PEDOT electrodes.

Carbon nanofibers (CNFs) are increasingly getting in the spotlight in bioanalytical area as through their properties of high surface area, non-toxicity and electrochemical stability. CNFs exhibit extraordinary strength and provide an extremely large surface area for electron charge transfer (compared to that of GO or PEDOT), making them a very promising candidate nanomaterial for recording and stimulation microelectrode sites [14]. We have recently combined PEDOT with CNFs as a single composite material on neural microelectrodes arrays (MEA). The PEDOT:CNF modified microelectrodes exhibit a low specific impedance of $1.28 \text{ M}\Omega\cdot\mu\text{m}^2$ at 1 kHz resulting in unrivaled charge injection limit of 10.03 mC/cm^2 when compared to other reported organic electrode nanomaterials. These results suggest the great potential of PEDOT:CNF composites for developing next-generation multifunctional bidirectional microelectrodes.

The focus of the present method is to provide a step-by-step protocol for the electrochemical synthesis of the composite material of PEDOT:CNF on neural MEA. The synthesis process is based on the use of oxidized CNFs as dopants of PEDOT through electrochemical deposition route, creating a nanocomposite in one step, localized on a $20 \mu\text{m}$ diameter microelectrode without

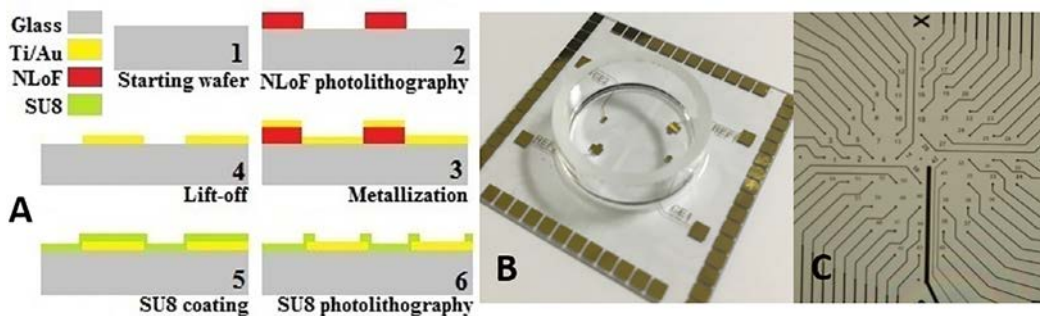


Fig. 1. MEA microfabrication. A) MEA microfabrication steps from the starting 4-in. glass wafer to the final SU8-coated wafer. B) Picture of a final functional MEA after glass well gluing. C) Optical picture of the microelectrode matrix.

the need of time-consuming grafting process. The combination of CNFs and PEDOT as a single composite material results in a strong synergetic effect between the two components leading to a superior microelectrode coating with remarkable electrochemical properties, combining as expected low impedance, high charge injection capability and reliable neurotransmitters monitoring using amperometric techniques.

Materials

NLoF 2035 and AZ-4562 photoresists were purchased from Microchemicals GmbH. SU8 2005, SU8 developer and MF CD26 developer were purchased from MicroChem. EDOT, dopamine, H_2SO_4 , Ethanol, Acetone, Tris buffer (15 mM Tris, 140 mM NaCl, 3.25 mM KCl, 1.2 mM $CaCl_2$, 1.25 mM NaH_2PO_4 , 1.2 mM $MgCl_2$, and 2.0 mM Na_2SO_4 , with the pH adjusted to 7.4), DA.2HCl were purchased from Sigma-Aldrich. CNFs were purchased from Sigma-Aldrich (Pyrograf[®]-III, PR-19-XT-PS, pyrolytically stripped, platelets conical, >98% carbon basis, 20–200 μm). In all experiments, deionized water (18 $M\Omega$) was used. Platinum and silver wires were purchased from WPI, Saturated Calomel Electrode (SCE) reference electrodes were purchased from Hach. Electrochemical characterizations were conducted with a 3-electrode electrochemical cell with a Pt wire as counter electrode and SCE as reference electrode. Electrochemical depositions were carried out with a 2-electrode cell using an Ag/AgCl wire as quasi-reference electrode, obtained by chlorination of a silver wire in 1 M HCl at 4 V vs Pt for 5 s. Stock solutions of dopamine were prepared in 0.001 M HCl and stored at 4 °C in the dark. This stock solution was used to prepare fresh dopamine solutions in Tris buffer before any experiment.

Microfabrication of microelectrodes array (MEA)

The MEAs chips were fabricated using a series of standard photolithographic steps (Fig. 1): 1) Glass wafer (4 inch) was cleaned in a Diener machine by MW-oxygen plasma (800 W, 5 min, 1000 sccm O_2) prior processing. 2) Spin-coating and photopatterning of a negative photoresist layer (NLoF, 5 μm) were performed onto the glass substrate. 3) PVD metallization of the wafer (Ti/Au, 50 nm/200 nm) and lift-off at room temperature in acetone overnight. 4) Wafer cleaning by piranha solution followed by MW-oxygen plasma (200 W, 400 sccm O_2 , 2 min). 5) Spin-coating and 6) photopatterning of a 1.5 μm -thick SU8 layer for passivation of the MEA, which is subsequently hard-baked to enhance its mechanical and barrier properties, while making it chemically more stable.

Once the lift-off process is done, the rugosity of both the metal tracks and the wafer are measured with a profilometer to detect irregular profiles that could be due to an incomplete lift-off and would prevent a uniform spin-coating of SU8 and its adhesion to the glass surface.

A combination of piranha and plasma cleaning after lift-off is used to ensure a complete cleaning of the wafer by removing organic residues and possible dust, while not damaging metal tracks with

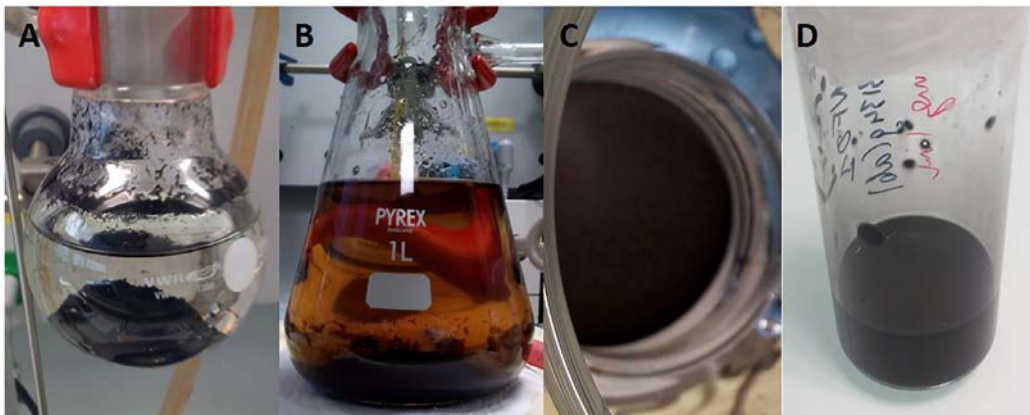


Fig. 2. CNF chemical oxidation. A) CNF Solution after cool-down and decantation steps. B) Filtration of the CNF solution on hydrophilic PTFE membrane. C) Picture of the final filtration cake of the PTFE membrane. D) CNFs dispersion at 2 mg/mL concentration in DIW.

high power MW-plasma treatment (which can overheat metals and induce crack/delamination) and still dehydrating and oxidizing the wafer surface before SU8 coating to promote its adhesion.

Hard-baking of the SU8 is realized by slowly ramping the wafer for room temperature to 125 °C and back at room temperature, in order to eliminate solvent traces from the polymer film and to obtain a complete cross-linking of the coating. Ramping temperatures is necessary to prevent mechanical stress inside the polymer film and at its interface with the glass.

Final packaging steps to obtain functional MEAs (Fig. 1B) were as followed: i) AZ-4562 10 μm spin-coating and baking on the entire wafer as a protective layer for dicing. ii) Diamond saw dicing of the wafer to release the MEAs. iii) Stripping of the protective photoresist layer in acetone (20 min). iv) glass well gluing with PDMS. v) PDMS curing at 60 °C for 3 h. vi) MEA conditioning in DIW overnight.

Preparation of carbon nanofibers

Raw CNFs could not be dispersed in water in an adequate manner for electrodeposition, even after extensive sonication on low CNF concentration (<0.5 mg/mL), as the solution showed decantation signs within 5 min after the sonication step. To circumvent this issue, chemical oxidation of the CNFs was performed, to make them hydrophilic and negatively charged. The experimental steps for this oxidation were as followed: 1) glassware cleaning by sonication in DIW/isopropanol (1:1 v/v) and dried overnight at 80 °C. 2) in a 150 mL-round bottom flask, 1 mg/mL of raw CNFs was dispersed in freshly mixed HNO_3 (68%)/ H_2SO_4 (96%) (3:1 v/v) by sonication (15 min, 90 s alternating pulsed and continuous sonication). 3) the solution is brought to reflux by heating at 70 °C under magnetic stirring (500 rpm) for 5 h. 4) the solution is let to cool down at room temperature overnight, for decantation (Fig. 2A).

Once the flask is cooled down, the solution is diluted in 1 L DIW and let sit overnight for decantation. The solution is filtered on hydrophilic PTFE membranes. The filtrated volume contains black particles and is dark-brown colored (Fig. 2B). The filtration cake (Fig. 2C) is rewetted and broken by slow addition of DIW and manual trituration with a metallic spatula. 250 mL of DIW are added and mixed with the wetted cake by agitation. This process is repeated until the filtrated volume remains clear after passing through the filtration membrane. Final filtration cake is removed from the PTFE membrane and kept in wet state to ease its redispersion. To estimate the water and CNF content in the final product, a small part of it is weighted and placed in a vacuum oven to dry at low temperature/low vacuum (45 °C, 300 mbar) until its weight reach a stable value. Oxidized CNFs are then dispersed in DIW at 2 mg/mL concentration and kept in the dark at 4 °C for storage (Fig. 2D).

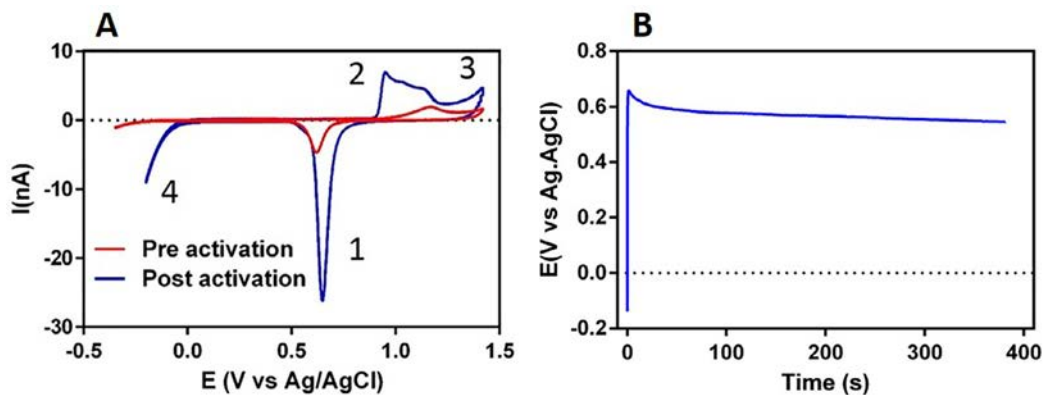


Fig. 3. Microelectrode activation. A) CV in H_2SO_4 0.5 M at 200 mV/s between -0.4 and 1.5 V, of a gold microelectrode ($20\ \mu\text{m}$ diameter) before and after activation (10 cycles of CA at 2 V for 250 ms and 0 V for 1 s). B) Voltammetric response of the microelectrode during deposition under constant current deposition.

Electrochemical deposition of PEDOT:CNF composite on microelectrodes and MEAs

To ensure good deposition conditions, microelectrodes must be cleaned. This is realized by electrochemical cleaning by a series of 10 potential pulse (2 V vs Ag/AgCl for 250 ms, 0 V vs Ag/AgCl for 1 s) in 0.5 M H_2SO_4 . Cyclic voltammetry is used to probe the microelectrode ($20\ \mu\text{m}$ diameter) state before and after the cleaning process (Fig. 3A).

As can be seen in Fig. 3A, the cleaning of the electrode can be observed through multiple changes in the CV: *i*) A shift toward the right of the reduction peak (which is also more resolved), meaning that less energy is necessary to gold oxide reduction, and by the higher reduction current observed, *ii*) the apparition of multiple oxidation peaks on the forward scan, more resolved than the starting one, and their shift toward the left, meaning less energy is necessary for gold oxidization, *iii*) the increase of current at 1.5 V, due to an increase of hydrolysis, meaning that the exposed surface has increased, *iv*) the apparition of the hydrogen sorption current at higher potentials, with a quicker increase, meaning the electrode state is compatible with hydrogen sorption on the electrode, phenomenon known to be inhibited by organic pollution.

For deposition, a solution of EDOT (10 mM) and CNF (1 mg/mL) is prepared. To ensure proper mixing, the solution is vortexed for 1 h after preparation and kept overnight at $4\ ^\circ\text{C}$ in the dark. Before use, the solution is revortexed for 30 min, sonicated for 10 min (pulsed, room temperature), and vortexed again for 5 min. The deposition solution is poured in the MEA right after activation of the microelectrodes. Electrode targeted for deposition is then submitted to a 3.14 nA current which is stopped when the deposition charge reaches 1200 nC (Fig. 3B). The deposition can be confirmed by both the presence of a quick (< 3 s) nucleation peak and the following decrease of the potential. It is worth mentioning that the potential reached during the electrochemical deposition (Fig. 3B) is far below the potential limit in water media, which may indicate that the electrodeposition method does not lead to an overoxidized PEDOT:CNF film. The deposition solution is gently re-homogenized in between multiple depositions by pipetting to redistribute in solution CNFs that could have been adsorbed of the MEA surface and improve deposition reproducibility.

Method validation

Scanning electron microscopy (SEM) and optical microscopy

The morphology of the PEDOT:CNF coating was confirmed by SEM using a HITACHI S-4800 cold FEG high resolution SEM with a voltage of 800 Vs and HIROX Numerical microscope. SEM images

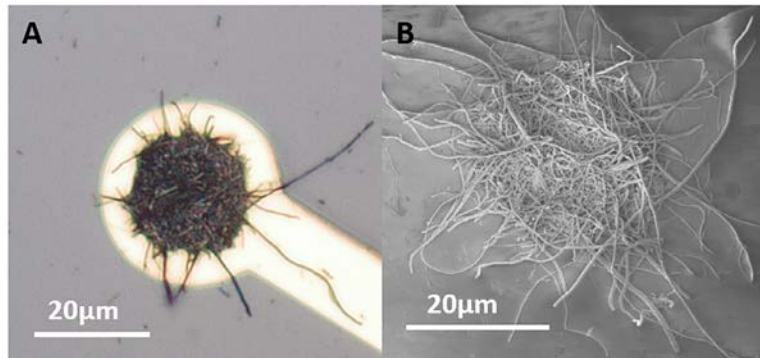


Fig. 4. PEDOT:CNF-modified microelectrode. A) Optimal picture and B) SEM image of a PEDOT:CNF-modified microelectrode.

Table 1

Comparison of the electrochemical performance of PEDOT:CNF microelectrode with some of the best nanostructured organic materials used to fabricate neural interfacing electrodes.

Electrode material	Geometric area (μm^2)	Specific impedance at 1 kHz ($\text{M}\Omega\cdot\mu\text{m}^2$)	Charge injection capacity ($\text{mC}\cdot\text{cm}^{-2}$)	Ref
PEDOT:PSS	4500	1.35	2.92	[19]
PEDOT:CNT	2830	42.45	1.25	[6]
PPy:PSS	12,467	24	5	[22]
PPy:CNT	12,434	25	7.5	[22]
PPy:Cl	12,240	34.5	3.2	[24]
CNT array	1962	5.9	1.6	[21]
CNT fiber	1450	20.44	6.52	[20]
Neat graphene fiber	1169	8.7	8.9	[22]
PEDOT:CNF	314	6.9	10.03	This work

confirmed that the PEDOT:CNF composite was uniformly distributed on the gold microelectrode with CNFs randomly distributed in the deposit (Fig. 4A and B). Oxidized CNFs act as dopant thanks to the negative charges on the fibers surface conferred by the chemical oxidation, behaving like counter anion to the conductive polymer PEDOT and the intermediary cation-radical during EDOT polymerization.

Electrochemical impedance spectroscopy (EIS)

EIS measurements ($N = 3$) were made through a Bio-Logic VMP3 potentiostat, by applying a 10 mV RMS sine wave with frequencies varied from 10 Hz to 7 MHz. The electrode active sites were immersed in artificial cerebrospinal fluid (aCSF). The mean impedance at 1 kHz for the unmodified gold microelectrode was around 2.8 $\text{M}\Omega$, while after PEDOT:CNF electrochemical deposition, the mean impedance fell to 20.1 $\text{k}\Omega$ (Fig. 5A). This confirms the ability of the modified microelectrode to be used as a recording electrode, with potential high SNR recordings due to its low impedance. The specific impedance of the PEDOT:CNF modified microelectrodes ($6.9 \text{ M}\Omega\cdot\mu\text{m}^2$ at 1 kHz) was *ca.* 130 times lower than gold microelectrodes ($898 \text{ M}\Omega\cdot\mu\text{m}^2$) and lower than the other reported organic electrode materials presented in Table 1. The Nyquist plot recorded in aCSF media is presented in Fig. 5B. In the higher frequency region, a semi-circle is observed which is related to the charge resistance between the electrode material and the surrounding electrolyte while at low frequencies the capacitive behavior becomes dominant. The incorporation of CNF in the PEDOT produced very small radius of the semi-circle on the Nyquist plot with a charge transfer resistance of about 14.2 $\text{k}\Omega$.

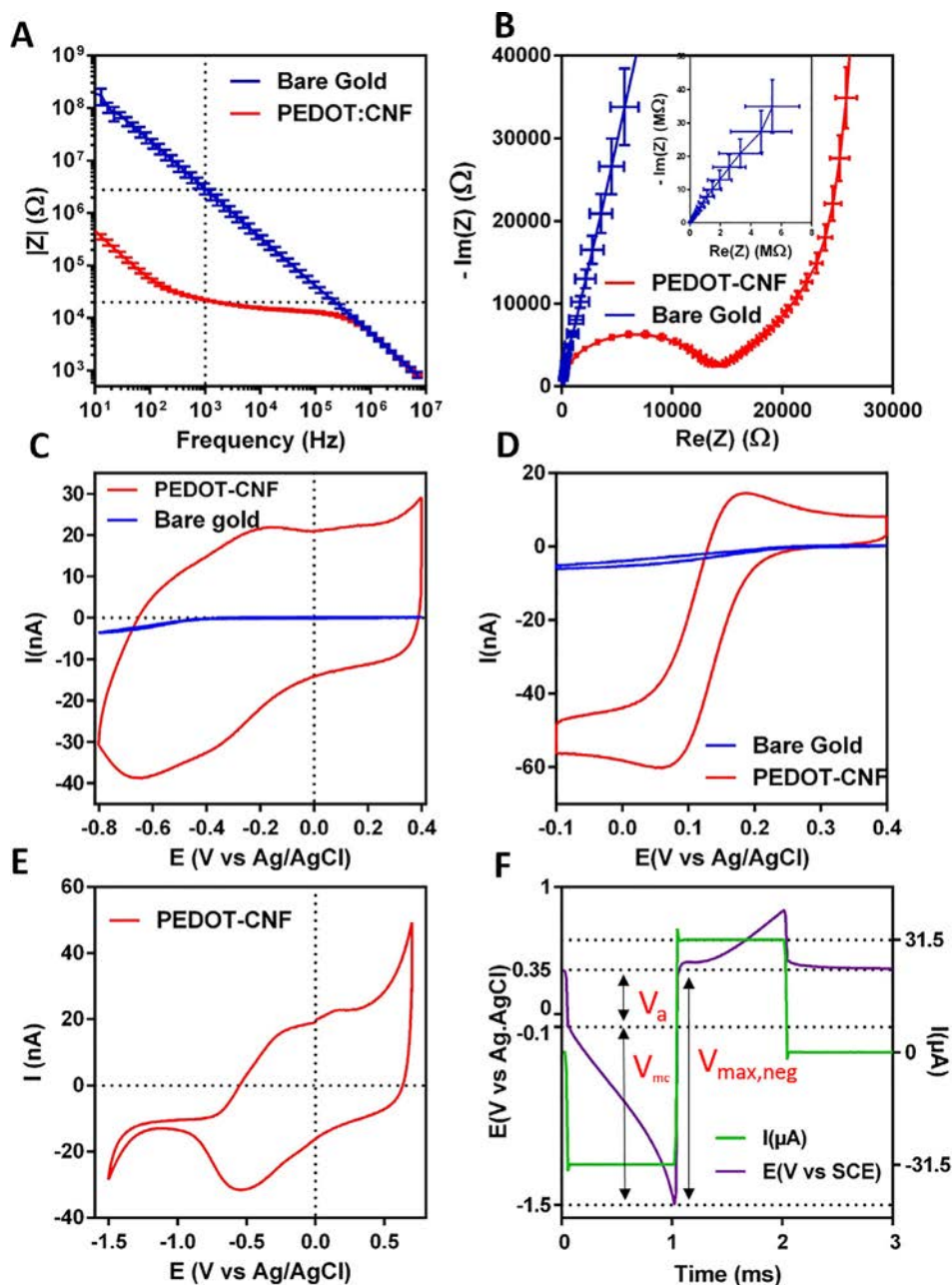


Fig. 5. Electrochemical characterization of PEDOT:CNF modified microelectrodes. A) EIS measurements on modified PEDOT:CNF and unmodified gold microelectrodes over a frequency range of 10 Hz to 7 MHz in aCSF vs Ag/AgCl at 10 mV ($N = 3$). B) Nyquist plots of modified PEDOT:CNF and unmodified gold microelectrodes over a frequency range of 10 Hz to 7 MHz in aCSF vs Ag/AgCl at 10 mV ($N = 3$). C) Cyclic voltammetry of modified PEDOT:CNF and unmodified gold microelectrodes in aCSF between -0.8 and 0.4 V vs Ag/AgCl. D) Cyclic voltammetry of modified PEDOT:CNF microelectrodes in 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ containing 0.1 M KCl at a scan rate of 200 mV s^{-1} . E) Cyclic voltammetry of PEDOT:CNF modified microelectrodes in a physiological media-mimicking buffer, Tris buffer 1X at $\text{pH}=7.4$, at 200 mV/s between -1.5 and 0.6 V vs Ag/AgCl. F) Typical stimulation current waveform (green trace) and total voltage excursion (purple trace) under the biphasic stimulation protocol (current pulse $I = 31.5$ μA).

Cyclic voltammetry (CV)

Cyclic voltammetry (CV) was carried out using a Bio-Logic VMP3 potentiostat, between -0.8 and 0.4 V vs SCE in aCSF at 200 mV/s. Deposits ($N = 3$) were cycled until a stable voltammogram was obtained, usually at the 4th cycle. The charge transfer capacity increased using PEDOT:CNF, as can be seen in Fig. 5C. The cathodal charge storage capacity (CSCc) of the composite film was calculated by the time integral of the cathodal currents within the cycled region, the CSCc of the bare gold microelectrode increased from 0.1 mC/cm² to 42.4 mC/cm² for PEDOT:CNF. This improvement is due to the higher surface area coating the PEDOT:CNF that allows effective diffusion of electrolyte ions at the electrode-solution interface, leading to a higher charge storage capability.

CV measurements were further performed in ferro-ferricyanide media. Ferri-ferrocyanide $[\text{Fe}(\text{CN})_6]^{3-/4-}$ is a standard inner-sphere redox couple used to evaluate the electrochemical properties of the electrode, particularly on carbon nanostructured surfaces. Fig. 5D shows the cyclic voltammogram of PEDOT:CNF microelectrodes in 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ containing 0.1 M KCl at a scan rate of 200 mV s⁻¹. A pair of quasi-reversible peaks is also observed, which can indicate that the conducting material PEDOT:CNF could accelerate the electron transfer between the electrochemical probe $[\text{Fe}(\text{CN})_6]^{3-/4-}$ and the PEDOT:CNF electrode. This result confirms the good electro-catalytic activity of the PEDOT:CNF electrode in the presence of ferro-ferricyanide media.

Voltage transient response

To characterize the performance of PEDOT:CNF microelectrodes for neural stimulation purpose, their responses when submitted to biphasic 1-ms current pulses were recorded *in-vitro* using a Bio-Logic VSP3 Potentiostat in a physiological media-mimicking buffer, Tris buffer 1X at pH=7.4. The microelectrodes were allowed to sit in the buffer media for 10 min before stimulation and the waveform was then applied. Voltage transients measurements were collected by the PEDOT:CNF microelectrodes using 1 ms-long biphasic current pulses with cathodic pulse first. Measuring the corresponding voltage excursion is employed to calculate the safe charge injection limits of the interface. These values correspond to V_{mc} (maximum negative polarization voltage) across electrode-electrolyte interface for PEDOT:CNF (Fig. 5F). The negative potential excursion V_{mc} was calculated by subtracting the access voltage (V_a), associated with the ohmic resistance of the electrolyte from the maximum negative voltage $V_{\text{max,neg}}$. [3] To ensure a safe polarization, the water window of the PEDOT:CNF microelectrodes in buffer solution was first determined using CV at 200 mV/s vs Ag/AgCl reference electrode (Fig. 5E). The water reduction and oxidation voltages were found to be at -1.4 and 0.6 V respectively. The polarization voltage V_{mc} was used to determine the CIL by increasing the pulse currents before V_{mc} is reaching the negative electrolysis frontier at -1.4 V. The measured corresponding maximum current before the water reduction potential was 31.5 ± 3 μA (Fig. 5F). The calculated charge injection was calculated at $V_{\text{mc}} = -1.3$ V, before the water reduction potential to be 10.03 ± 1 mC/cm² for the PEDOT:CNF microelectrodes. The calculated CIL of the composite material was compared to some other reported organic materials (Table 1).

Amperometric detection

Electrochemical detection of dopamine (DA) was performed by chronoamperometry at 130 mV vs SCE after this potential was identified previously as the oxidation potential of DA on PEDOT:CNF by CV [17]. The DA direct current responses ($N = 3$) resulted in calibration plot *i.e.* amperometric current response vs different concentration of DA with correlation coefficients >0.999 (Fig. 6). The corresponding sensitivity were calculated as 13.4 pA/ μM with the limit of detection (LOD) of 0.045 μM . In terms of concentration ranges, these LOD were well suited to the reported assay of these analytes in the medical field [15].

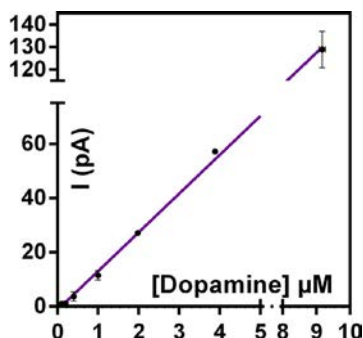


Fig. 6. Linear regression curve of PEDOT-CNF microelectrode current response at 130 mV vs SCE to dopamine injections. The currents steps in the figure correspond to stepped concentrations increase from 0 to 9 μM .

Conclusions

We have described a step-by-step protocol for the electrochemical synthesis of a novel composite material of PEDOT-CNF on microelectrodes array by a simple and reproducible electrodeposition method. The results from this study suggest the great potential of PEDOT:CNF composites for developing next-generation microelectrodes for applications in neural therapies and biomedical research by taking advantages of its multifunctionality.

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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.

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