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# Microfabrication, characterization and in vivo MRI compatibility of diamond microelectrodes array for neural interfacing



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#### ARTICLE INFO

Article history: Received 18 June 2014 Received in revised form 24 September 2014 Accepted 2 October 2014 Available online 5 October 2014

Keywords: Diamond Neural interface MRI compatibilty Microelectrode array

#### ABSTRACT

Neural interfacing still requires highly stable and biocompatible materials, in particular for in vivo applications. Indeed, most of the currently used materials are degraded and/or encapsulated by the proximal tissue leading to a loss of efficiency. Here, we considered boron doped diamond microelectrodes to address this issue and we evaluated the performances of a diamond microelectrode array. We described the microfabrication process of the device and discuss its functionalities. We characterized its electrochemical performances by cyclic voltammetry and impedance spectroscopy in saline buffer and observed the typical diamond electrode electrochemical properties, wide potential window and low background current, allowing efficient electrochemical detection. The charge storage capacitance and the modulus of the electrochemical impedance were found to remain in the same range as platinum electrodes used for standard commercial devices. Finally we observed a reduced Magnetic Resonance Imaging artifact when the device was implanted on a rat cortex, suggesting that boron doped-diamond is a very promising electrode material allowing functional imaging.

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## 1. Introduction

Microelectrode arrays (MEAs) are powerful devices for in vivo and in vitro neural interfacing. They are now used in a wide range of applications from basic research on cultured neural network to the development neural prosthesis in human patients [1–3]. Such a high interest is supported by the development of advanced electrode materials that offer biocompatibility, low noise and large charge injection limit along with high temporal and spatial resolutions. However, there is still a great need for highly stable and biocompatible materials for chronic application [4,5]. Indeed, most of the current electrode materials are degraded by the biological medium and/or encapsulated by a cell layer composed of different types of glial cells that usually develop after a mechanical insult of the neural tissue [5-7]. Such biological coatings strongly affect both reliability and stability of the electrodes and in particular increase their impedance [8]. Finally, given the increasing contribution of Magnetic Resonance Imaging (MRI) for brain investigations in both animals and humans, any microelectrode that is aimed at

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being implanted in the brain should not generate any magnetic field distortion. Ideally, this implies that no part of the device should have a magnetic susceptibility above that of water [9].

In such a context, boron-doped diamond appears today as a very promising material. Actually since the first report of neuron culture on single crystal diamond in 2004 [10], several studies showed the high biocompatibility of oxygen-terminated diamond and boron doped diamond material [11–13]. In particular, those studies highlighted that diamond is a good candidate for long-term neural interfacing [12]. Moreover, diamond is supposed to induce relatively low MRI artifacts because of the low magnetic susceptibility of carbon, which is near to that of water [14]. In addition, the use of diamond for neurotransmitter sensing has already been reported to present promising properties [15–19]. Yet, few diamond-based devices for electrical neural interfacing have been reported [20-25]. Here, we investigated the potentials of boron-doped diamond microelectrodes for electric neural interfacing using a homemade 121 microelectrodes diamond prototype with addressable array. The array was first characterized by electrical impedance spectroscopy to verify that the electrical properties of the electrodes and the insulating layer are sufficient to operate in the biological band frequencies. Cyclic voltammetry in FeCN<sub>6</sub><sup>3-/4-</sup> was also performed to check the presence of pinholes in the matrix. Then cyclic

voltammetry and electrochemical impedance spectroscopy were carried out in Phosphate Buffered Saline (PBS) to estimate the charge storage capacitance (CSC) and the impedance modulus of boron doped polycrystalline diamond (B-PCD) electrode for stimulation and recording. Finally the compatibility of boron-doped diamond with MRI studies was assessed in vivo by implanting five  $3 \times 3$ mm boron-doped diamond prototypes on the cortical surface of three adult rats. MRI scans performed two and six months after the implantation revealed reduced artifact.

# 2. Materials and method

# 2.1. MEA microfabrication

The first step of the MEA fabrication process (all the microfabrication steps are summed up in Fig. 1) consisted in growing the insulating diamond layer on a 2" silicon wafer (Fig. 1.1) in a commercial microwave plasma reactor (Seki Technotron, AX 5200). This included the diamond nucleation using the so-called bias enhanced nucleation technique [26] as well as the growth of a 1  $\mu$ m thick intrinsic diamond layer (Fig. 1.2). The transverse resistivity of the film was measured to be 0.2 T $\Omega \cdot$ cm. The parameters of the nucleation and of the insulating diamond growth are given in Table 1.

A 1- $\mu$ m thick B-PCD layer was then grown on the insulating layer in a homemade NIRIM type Microwave Plasma Chemical Vapor Deposition (MPCVD) reactor (Fig. 1.3). The parameters for the growth of the boron-doped diamond layer are given in Table 2. We estimated the boron concentration in the crystal to be in the range of 2.10<sup>21</sup> cm<sup>-3</sup> by Raman spectroscopy (at 632 nm), which is above observed metallic transition on monocrystalline diamond [27].

We etched the conductive diamond layer by plasma to reveal the patterns of the microelectrodes, the conductive tracks and the contact pads. An 80-nm thick nickel layer deposited by metallic evaporation was used as a mask (Fig. 1.4). We performed this plasma etching in an Inductive Coupled Plasma reactor with oxygen plasma at low bias voltage in order to reduce the sputtering of the metallic mask (Fig. 1.5).

#### Table 1

Parameters used for the nucleation and the growth of the insulating layer in the Seki reactor (D stands for duration, DC for bias).

	P(Torr)	T(°C)	C/H(%)	P(W)	D(min)	Bias(V)
Nucleation	16	700	5	1400	7	×260
Growth	30	1100	0.5	1300	480	х

Finally, we electrically insulated the connections via a selective growth of an insulating diamond layer above the metallic path (Fig. 1.6). Several teams already reported selective growth techniques on diamond [28, 29]. Here the active areas (microelectrodes and contact pads) of the microelectrode array were covered with a silicon dioxide layer of 1.8 µm followed by a chromium layer of 200 nm deposited by cathodic sputtering (Fig. 1.7). The samples were transferred afterwards in a NIRIM type reactor to perform growth of the last insulating diamond layer. The sacrificial layers were finally removed by a commercial chromium etchant and fluorhydric acid (Fig. 1.8).

The surface of the top insulating diamond layer was intrinsically hydrogen terminated. This induced a surface conduction that connected all the electrodes together [30]. The sample was thus immersed in an ozone atmosphere to passivate the surface [31]. Finally, the contact pads were covered with titanium, platinum and gold allowing a proper binding and avoiding the passivation of the contact.

#### 2.2. Implant preparation

We deposited boron-doped diamond films of 1  $\mu$ m on 350- $\mu$ m thick boron doped silicon substrate (3 × 3mm<sup>2</sup>). We then thinned the silicon thickness down to 100  $\mu$ m by KOH etching.

#### 2.3. Electrochemical characterization

We performed cyclic voltammetry and electrochemical impedance spectroscopy with a VSP 300 potentiostat from Biologic, interfaced by the EC-lab software. Two solutions were used to characterize the



Fig. 1. Schematics of the all diamond MEA fabrication process.

#### Table 2

Parameters for the growth of the 1  $\mu m$  thick boron doped diamond layer (doping level in the layer  $\approx 2 \cdot 10^{21}$  cm^{-3}).

	P(Torr)	T(°C)	C/H(%)	B/C(ppm)	P(W)	D(min)
Growth	30	890	0.5	2400	290	180

electrode. First, the measurements were performed in the presence of the  $Fe(CN)_6^{3-/4-}$  standard redox couple at a concentration of 6 mM in PBS. This fast redox couple is actually commonly used to evaluate the electrochemical reactivity of an electrode [19]. Second, we used PBS alone as an electrolyte to determine the double layer capacitance, the charge storage capacity (CSC) as well as their electrochemical impedance in a biological-like medium.

#### 2.4. Implantation surgery

All experiments were performed in accordance with the rules of the European Committee Council Directive 86/609/EEC after validation by our local ethical committee in Grenoble. All efforts were made to minimize animal suffering and reduce the number of animals used in each series of experiments. Three male Wistar rats (4 months; 350–400 g) underwent surgery under ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) general anesthesia. They were placed in a stereotaxic frame and bilateral  $4 \times 4$  mm windows were drilled on the skull of each rat using the following coordinates (A/P: -1 to -5 mm; ML  $\pm 1$  to  $\pm 5$  mm, from bregma). The dura mater was removed to position  $3 \times 3$  mm implants in direct contact with cortical surface, diamond side facing brain tissue. Windows were then closed with cyanolate gel paste. Skin was then sutured and animal's general behavior was monitored every week following the surgery for up to one month.

# 2.5. MRI acquisitions

We assessed impact of boron-doped diamond samples ( $3 \times 3$ mm) mimicking MEA material two and six months after surgical implantation. Magnetic resonance images were acquired on a horizontal 4.7 T MR scanner (Avance III console; Bruker, Germany; IRMaGe MRI facility, La Tronche, France) with a gradient coil capable of generating 660 mT m<sup>-1</sup> with a 114-µs rise time. Radio Frequencies signals were transmitted with a linearly polarized volume coil (internal diameter 72 mm, Bruker, Ettlingen, Germany), and recorded using a quadrature surface receive RF coil (Rapid Biomedical, Rimpar, Germany). Both coils were actively decoupled. A local second order shim was performed in the rat brain.

Structural T<sub>1</sub> and T<sub>2</sub>-weighted images were acquired in coronal plane using a RARE T<sub>1</sub> sequence (TR 1 s, TE 6.5 ms, voxel size 117 × 117 × 1000  $\mu$ m<sup>3</sup>, FOV 30 × 30 × 12 mm<sup>3</sup>) and a TurboRARE T<sub>2</sub> sequence (TR 5 s, TE 20 ms, voxel size 137 × 137 × 1000  $\mu$ m<sup>3</sup>, FOV 35 × 35 × 25 mm<sup>3</sup>) to localize the implants. B<sub>0</sub> distortions were assessed by a high-resolution field map acquired using a dual-echo 3D gradient-echo sequence (TE<sub>1</sub> 1.8 ms, TE<sub>2</sub> 5.8 ms, TR 20 ms, FA 20°, (273  $\mu$ m)<sup>3</sup> isotropical voxels, FOV 35 × 35 × 70 mm<sup>3</sup>).

#### 3. Results and discussion

The diamond microelectrode array is presented in Fig. 2. Fig. 2a shows a picture of the device and a SEM image of the whole 121 B-PCD microelectrodes. Fig. 2b is a SEM image with a higher magnification of one of the electrodes. The conductive diamond electrode in dark gray can be clearly distinguished from the insulating diamond layer in light gray due to the difference of electronic conductivity of the two materials. Fig. 2c is a cross section of the conductive tracks. The conductive diamond can also be easily distinguished from the insulating diamond



Fig. 2. a: Global view of the diamond MEA; b: SEM image of a boron doped microelectrode and c: cross section of the boron doped tracks encapsulated in the intrinsic diamond layer.

shell. Such a large SEM contrast is already an indication of the good insulation of the boron-doped diamond by the intrinsic layers.

Since this MEA should be able to operate with signal frequencies up to 10 kHz and allow recording sampling up to 50 kHz [32,33], it was mandatory to verify that very few current will diffuse from the conducting to the insulating part in this frequency range. We thus performed electrical impedance spectroscopy on the insulating layer and on the electrodes in series with the tracks in order to assess their electronic conduction. Fig. 3a and b shows the Bode spectra of the tracks and of the top diamond insulating layer respectively. The sketches above the spectra represent the experimental set-up for each measurement. The Bode spectrum of the insulating layer showed a constant impedance modulus of 10 M $\Omega$  and a phase near to 0 between 10 Hz and 10 kHz. This indicated that the insulating layer acts as a pure 10-M $\Omega$  resistance in this frequency range. Then, the impedance modulus decreased steadily at 100 kHz to reach 1 M $\Omega$  at 1 MHz. The electrical impedance of the boron-doped electrodes in series with the tracks was mainly resistive until 100 kHz, showing a resistance of 3.8 k $\Omega$ . Hence the impedance modulus of the insulating layer was at least three orders of magnitude higher than the conductive tracks on the whole frequency range. Considering that biological band frequencies are generally limited to 10 kHz, it can be inferred that insulating properties of diamond layer were sufficient enough to offer a good electrical insulation and to insure the reliability of the electrode for biological applications. We then search for pinholes in the insulating layer to detect any unwanted active zone on the device. Very few techniques are available to detect pinholes in the passivation layer [34,35]. One of the most accurate and quickest consists in measuring of the limiting current given by a microelectrode. Indeed, the approximate active surface area can be determined with the theoretical limiting current in presence of a redox couple given by the following formula [36]:

 $I_{lim} = 4nrFD_{redox}C$ 

where  $D_{redox}$  is the diffusion coefficient of the redox couple in water, F is the Faraday constant (96485 sA·mol<sup>-1</sup>), r is the electrode radius, n is the number of electrons exchanged between the electrode and the redox couple and C is the concentration of the redox couple. We measured the limiting current by cyclic voltammetry with FeCN<sub>6</sub><sup>3-/4-</sup>. Fig. 4a shows the standard sigmoïdal shape voltammograms of a microelectrode with the presence of cathodic and anodic limiting currents corresponding to the diffusion of the reactive species at the electrode surface. This shape first confirmed the micrometric size of the active surface. Moreover the limiting current was around 40 nA compared to a theoretical value of 46 nA ( $D_{redox} = 6.67.10^{-6} \text{ cm}^2 \cdot \text{s}^{-1}$ ). This indicates that the electrodes are the only active sites in contact with the liquid and that the subsequent electrochemical properties of the B-PCD electrodes can be accurately derived.

We thus evaluated the performance of B-PCD electrodes ( $\emptyset$ 60 µm) for the neural stimulation. Stimulation electrodes should have high double-layer capacitance and high charge injection limit in PBS. Double-layer capacitance can be derived from the capacitive current obtained by cyclic voltammetry according to the following formula:  $C = \frac{\Delta i}{2v}$ where  $\Delta i$  is the difference between the anodic and cathodic current at a potential where no faradic current is recorded and v is the scan rate. Likewise, the CSC can be derived from the capacitive current by integrating the cathodic or the anodic current through the whole potential window of the electrode. Cyclic voltammetry of the diamond microelectrodes is presented in Fig. 4b. They exhibit a wide potential window of 3.2 V with an average background current of 0.25 nA at 130 mV  $\cdot$  s<sup>-1</sup>. The corresponding values of the double layer capacitance and charge storage capacity were 70  $\mu$ F·cm<sup>-2</sup> and 435  $\mu$ C·cm<sup>-2</sup> respectively, which is coherent with a previous study where a double layer of  $85 \,\mu\text{F} \cdot \text{cm}^{-2}$  was reported [22]. Such values are comparable to the  $350 \,\mu\text{C} \cdot \text{cm}^{-2}$  obtained on platinum electrodes already used for neural stimulation [37]. Nevertheless they are larger than the typical 5- $7 \,\mu\text{F} \cdot \text{cm}^{-2}$  usually obtained on boron-doped diamond materials. This can be explained by the contribution of sp2 bounds [38]. To comfort this hypothesis we performed Raman spectroscopy mapping on the B-PCD microelectrode using a Jobin-Yvon T64000 spectrometer. The excitation wavelength was the 514.5 nm line of an argon ion laser. A 70  $\times$  70  $\mu$ m<sup>2</sup> area was mapped with a 1  $\mu$ m point spacing using  $a \times 100$  objective. Fig. 5 shows the mean spectrum derived from 225 spectra recorded over one particular diamond microelectrode. The typical boron doped diamond spectrum can be clearly identified with the peaks at  $1210 \text{ cm}^{-1}$  and  $1300 \text{ cm}^{-1}$  [39]. The weak shoulder at about and 1332  $\text{cm}^{-1}$  is most probably due to the underlying undoped material. Finally, the lines at 1350  $\text{cm}^{-1}$ , 1540  $\text{cm}^{-1}$  and 1583  $\text{cm}^{-1}$  are the signature of graphite and amorphous sp<sup>2</sup> phases [39]. This observation confirms the hypothesis of the presence of some sp<sup>2</sup> bound most



Fig. 3. Impedance characterization of the insulating and conductive diamond. a: Bode representation of the impedance of the conductive track. b: Bode representation of the impedance of the insulating layer. The red lines in the insights show the position of the contact for the impedance measurement. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Fig. 4. Cyclic voltammetry on boron doped polycrystalline diamond electrode ( $\emptyset 60 \ \mu m$ ) in a) Fe(CN) $\frac{3}{6}^{-/4-}$  6 mM in PBS 0.2 M and b) PBS 0.2 M.

probably located at grain boundaries that contributes to the large double layer capacitance of our microelectrodes.

We then characterized the interfacial electrochemical impedance of the B-PCD in PBS. Interfacial electrochemical impedance optimization in a biological medium is a critical issue for microelectrodes in neural tissue environment. It should be as low as possible during recordings to provide a good signal-to-noise ratio and to avoid signal distortion by the application-specific integrated circuit (ASIC). Many data were reported on interfacial impedance of diamond microelectrodes in  $Fe(CN)_6^{3-/4-}$  but very few are available in biological-like medium. In this respect we performed electrochemical impedance spectroscopy on our B-PCD microelectrodes in PBS. Fig. 6 shows the Bode spectrum recorded between 0.1 Hz and 200 kHz at open circuit potential with sine amplitude of 10 mV. It presents a charge transfer resistance of  $40 \text{ M}\Omega$  in low frequencies revealing that no electrons are transferred between the PBS and the electrode. a cut off frequency at 10 Hz and an impedance modulus of 400 k $\Omega$ . Such an electrochemical impedance spectrum shape is in line with the values obtained for platinum electrodes already used for stimulation and recording [40].

In the last experiment, we investigated the compatibility of borondoped diamond with MRI scanning. We implanted boron-doped diamond films deposited on silicon substrate ( $3 \times 3$ mm) to mimic the MEA material on the cortical surface of three adult rats. Fig. 7 shows coronal sections of T<sub>1</sub>-weighted brain MRI scans through the position of the diamond samples, two and six months after implantation, as well as images of B<sub>0</sub> distortions observed at six months. Implants did not affect the MR signal and were only slightly visible on all MR images, both at two and six months after implantation. At two months, a subcutaneous



Fig. 5. Mean Raman spectrum on B-PCB microelectrode.

inflammatory reaction due to surgery was still visible on the structural images, but was not apparent anymore after six months. No major alteration of brain tissue around the implant was visible on MRI scans.  $B_0$  maps did not reveal any significant field distortions around the implant and  $B_0$  variations were much smaller than those observed at the base of the brain and due to deoxy-hemoglobin in internal jugular veins. This suggests that boron-doped diamond did not induce MRI artifacts and could be used for MRI.

# 4. Conclusion

We evaluated here electrical and electrochemical properties of all diamond microelectrode arrays for multisite recording or stimulation. We showed that it is possible to bring together very resistive and metallic diamond to build a functional and addressable diamond array. Electrochemical characterizations showed that B-PCD electrodes have the same properties than platinum electrodes that are already used for neural recording and stimulation. Our in vivo MRI scans of B-PCD implants confirmed their excellent compatibility with this technique. Indeed, we saw no MRI artifacts around the boron-doped diamond and substrate. Our results show that our diamond electrodes already fulfill all the requirements for in vivo and in vitro neural interfacing. Integrating structured diamond material on MEA would certainly improve biocompatibility of neural interfacing and should be considered to develop new devices for studies involving MRI scanning.



Fig. 6. Electrochemical impedance spectroscopy on a diamond microelectrode ( $\phi = 60 \,\mu m$ ) in PBS.



**Fig. 7.** T<sub>1</sub>-weighted coronal sections passing at the position of the diamond samples, two (a) and six (b) months after the implantation on the cortex. (c) Maps of B<sub>0</sub> distortions observed at six months. The red circles indicate the position of the implants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

### Acknowledgments

The authors would like to thank Tanguy Chabrol for his technical help and Catherine Villard for the design of the MEAs.

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