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An electrostimulation cell device with patterned $\text{TiO}_2\text{:Nb}$ thin films as bio-electrodes

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ABSTRACT

We present a cellular test device based on Nb:TiO_2 (niobium doped titania) transparent conductive oxide (TCO) as bio-electrodes. The device is intended to easily provide electrical stimuli to a given cell tissue and to monitor its response. The Nb:TiO_2 thin film deposition were performed with combinatorial chemical beam epitaxy (C-CBE) which allows for linear and well controlled gradients of both Nb concentration (ranging from 3% to 10%) and oxide thickness in predefined directions (usually orthogonal). We have systematically characterized the Nb:TiO_2 films with Atomic Force Microscopy, Scanning White-light Reflectometry, and sheet resistance. Finally, we show the device, i.e. the electrodes design and patterning in order to perform to electrical stimuli to the various ways to measure the cell's response.

Keywords: Transparent conductive oxide (TCO), doped titania, cell culture, bio-electrode, white-light reflectometry

1 INTRODUCTION

We are looking for a biocompatible and versatile (in terms of electrical sheet resistivity) transparent conductive oxide which can be used as thin electrodes in biomedical devices. Indeed, the most common TCO, namely ITO (indium tin oxide) is not convenient because of its poor biocompatibility and its predictable lack of availability at a reasonable price in the near future (indium). Titania (TiO_2) based materials, on the other hand, appear as a prime choice as TiO_2 is the flagship material in term of biocompatibility. Its large band gap (3eV) makes it optically transparent in the visible range: as a consequence, the device can be used under an epi-fluorescence microscope during the test, which is very valuable in most experiments. Titania is a highly resistive material which can be made electrically conductive with a small concentration of Nb (1) ranging from 2% to 10%, i.e. up to the limit of solubility. Nb doping atoms are substitutional to Ti atoms in anatase phase. Conductivity of typically $0.4 \mu\Omega\text{cm}$ has been reported (2) which makes Nb:TiO_2 competitive to ITO

In this research, we aim to design a versatile device which can be used to study the electro-stimulation of

various cell cultures, typically neurons or cardiocytes. Titanium dioxide has already been reported to be a convenient material to promote neural cell growth (3).

2 FABRICATION OF THE DEVICE

2.1 Films of $\text{TiO}_2\text{:Nb}$ by CVD

Chemical Beam Epitaxy (CBE) is a UHV thin film deposition technique that enables various types of gradients such as chemical and thickness gradients. Its working principle (Fig. 1) is to flow one or several gas of molecular precursors in the chamber, with molecules distributions that are inhomogeneous in a very well controlled way. When the precursor molecules react with the heated substrate (again with a controlled temperature distribution) at a specific substrate location, the film will grow at a rate depending on the substrate temperature and with a chemical composition depending of the precursor concentration at this location. As a result, a very large number of films parameters can be synthesized in a single wafer (4'' in our case). This so-called combinatorial approach is very efficient to find the optimal film properties for a given application.

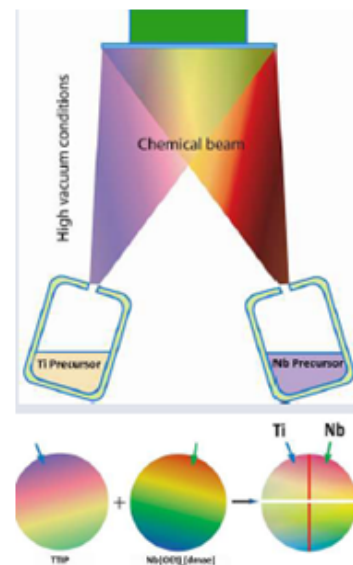


Figure 1: Schema of CBE with explanation of the gradient

2.2 Electrodes design and etching

The bio-electrodes pattern is shown in Fig. 2a). It consists of three spatially separated patterns, each containing three set of electrodes. The two outer sets of electrodes (i.e those not connected each other) are intended to measure the effects of a *dc* or *ac* electric field on the cell, while the inner set of electrodes (connected by a channel in the middle) can be used the measure the effect of a *dc* or *ac* electric current. We first produced standard metallic electrodes (such as aluminum or Au/Cr) in order to have a control, as Au is the material standard for this application. For the final device, we have used Nb:TiO₂ electrodes deposited by CBE with the optimal Nb concentration. An example of such deposited electrodes on 4'' glass wafer is shown in Fig 2b).

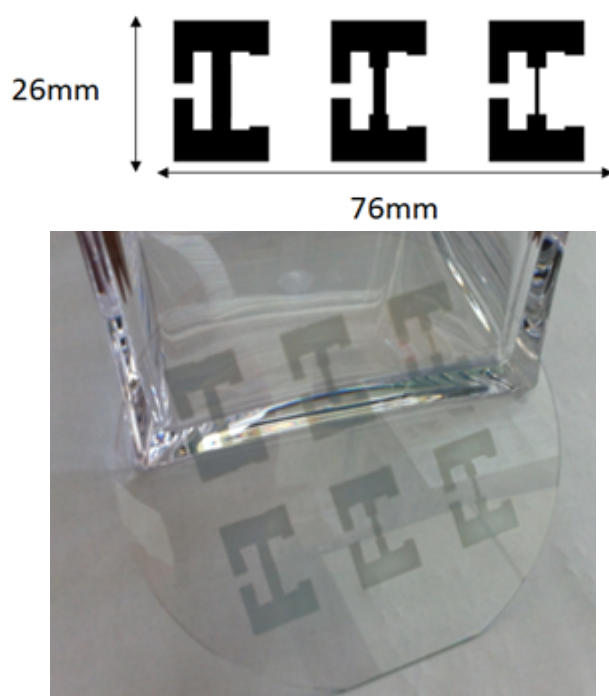


Figure 2: a) Pattern of the electrodes, b) Picture of the Nb: TiO₂ electrodes on a 4 inch glass wafer

2.3 Encapsulation and electric contacts

The encapsulation of the bio-electrodes on the final device is shown in Fig. 3. Apart from the integrated circuit (shown in green in Fig 3)), the other layers are made from 1mm thick PMMA layers. The fluidic channels and the openings in the PMMA layers have been made by laser machining with a CO₂ laser. The assembled device is placed in an incubator and electrically connected sine wave generator. Typical signals were 50mVpp at 1 Hz.

On the final version, the device is placed in an incubator and the electrical impedance is measured continuously during the incubation time.

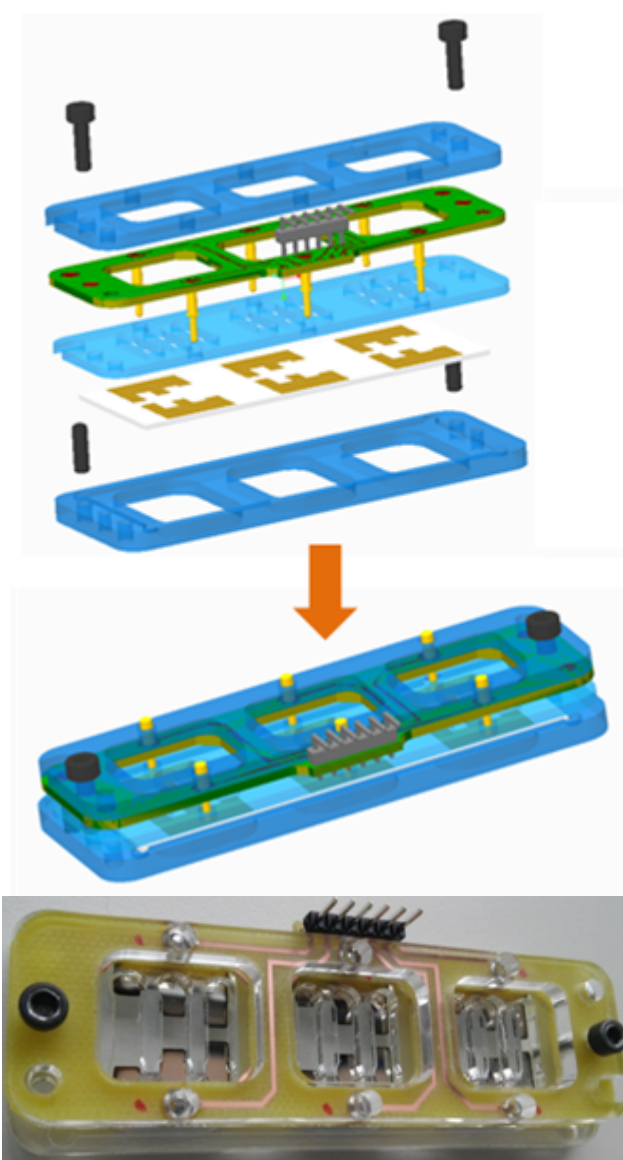


Figure 3: a) CAD view and b) picture of the device

3 ELECTRODES CHARACTERIZATION

As explained above, we have used a combinatorial approach for the Nb:TiO₂ thin film deposition. The full 4'' wafer then has to be investigated, requiring a full-wafer metrology instrument. We have developed such an instrument (see Ref (4)) which allows for various characterizations on the full wafer, including the optical thickness and the sheet resistivity

3.1 Scanning white light interferometry

The optical thickness nd (n is the refractive index and d is the thickness) can be obtained with the white light reflectivity spectrum. Representative results on Nb:TiO₂ films is shown in Fig 4 and Fig 5), for homogeneous thicknesses and graded thicknesses respectively. We can see the ability of the C-CBE system to produced very well controlled thickness, from 30nm to 3um, over the 4 inch of the wafer.

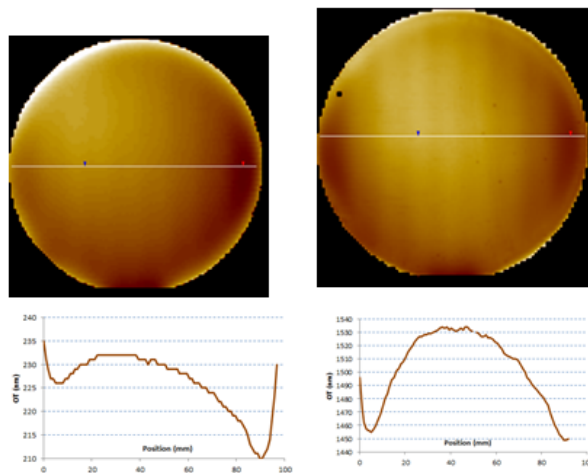


Figure 4: Optical thickness for homogeneously thick samples. A) thin sample B)thick sample

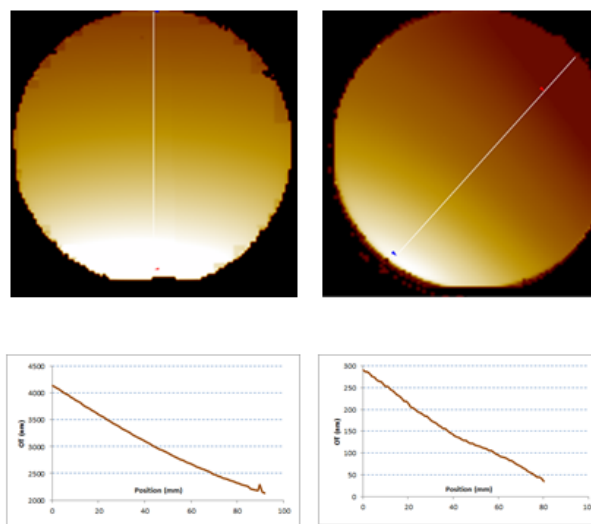


Figure 5: Optical thickness for graded thicknesses A) thick sample B) thin sample



Figure 6: Optical thickness of the end-product Nb:TiO₂ electrodes

Fig. 6 shows the optical thickness of a bio-electrodes actually used for the biological test. The black to white scale ranges form 214nm to 275nm.

3.2 Sheet resistance

The mapping of the sheet resistance has been done with a 4 probes electrical head installed in plce of the optical fiber in our full wafer metrology system. A representativer result is shown in Fig 7 for film with ahomogeneous thickness.

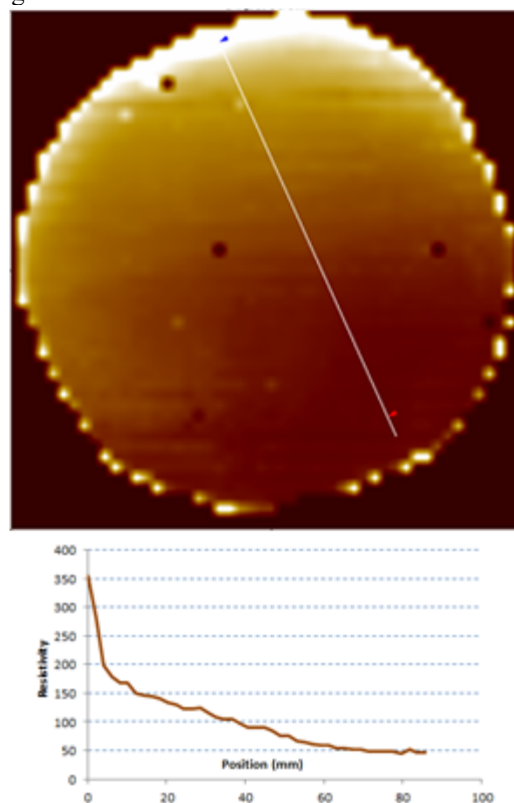


Figure 7: Sheet resistance over the full wafer for an homogeneous thickness Nb:TiO₂ film.

4 CELLS IN ELECTROSTIMULATION

Fig. 8 shows a first biological test performed on the bioelectrodes and devices reported here. We have used neural ReNcells, either with (left part of the Fig) our without (right part) electrical stimulation.

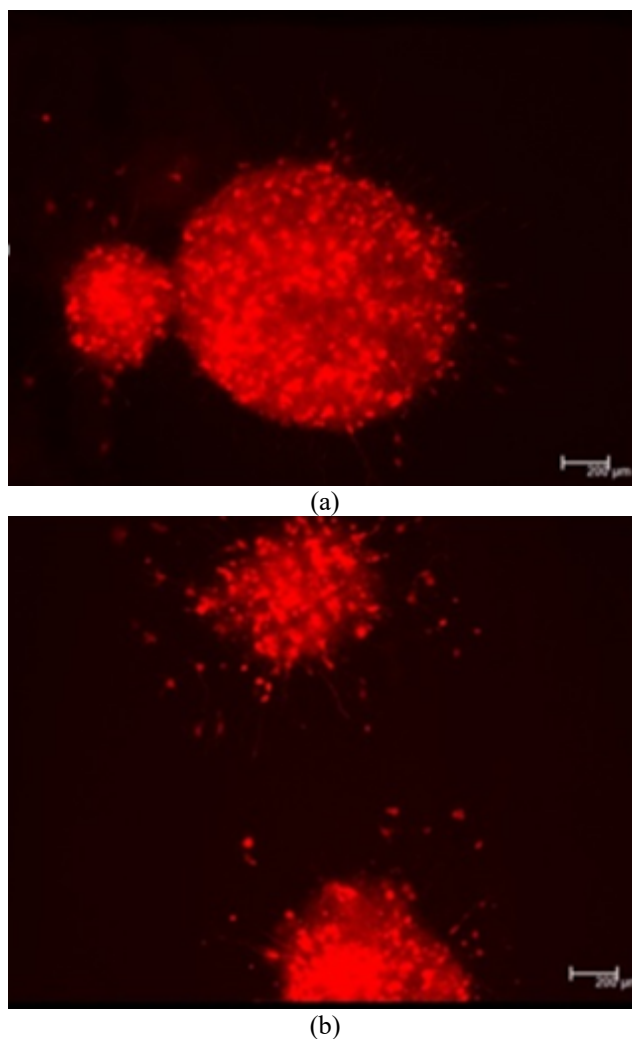


Figure 8: Fluorescence optical microscopy of RFP-ReN cells. 5 days after seeding with **a)** electrical stimulation or without

b) electrical stimulation. Scale bar : 200um.

These are florescence confocal microscopy images taken after 5 days on incubation. We can see that the influence of the electrostimulation on the growth of neural cells. The experiments have shown that the Nb:TiO₂ deposition is not toxic but do not allow ReNcells to attach very well so far.

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