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## Enabling a bidirectional communication between artificial and biological neurons using a novel neurobiohybrid interface

Nathan Schoonjans<sup>1</sup>, Virginie Hoel<sup>1</sup>, Dimitri Henniquau<sup>1</sup>, Vanessa Avramovic<sup>1</sup>,  
Mohamed Bellaredj<sup>1</sup>, Pascal Mariot<sup>2</sup>, Valerio Farfariello<sup>2</sup>, David Delcroix<sup>1</sup>, Redha Kassi<sup>1</sup>,  
Alain Cappy<sup>1</sup>, Alexis Vlandas<sup>1</sup>, Christel Vanbesien<sup>1</sup>

1. Univ. Lille, CNRS, Centrale Lille, Univ. Polytechnique Hauts-de-France, UMR 8520 - IEMN - Institut d'Electronique de Microélectronique et de Nanotechnologie, F-59000 Lille, France
2. Univ. Lille, Inserm, U1003 - PHYCEL - Physiologie Cellulaire, F-59000 Lille, France

### INTRODUCTION

Over the last decade, significant advances have been achieved in deciphering the biology of neuronal networks, thus enabling a better understanding of human brain function. The physical properties of biological neuronal networks have inspired the development of artificial systems thus setting the bases for the emerging field called neuromorphic engineering. The knowledge acquired in neurosciences has enabled to design smart systems able to learn by mimicking the communication behavior of biological neurons. Such neuromorphic systems are the heart of the ongoing revolution in the field of artificial intelligence (Merolla et al., 2014). In parallel, the research field of neurobiohybrid systems aiming to improve or restore impaired neuronal functions has rapidly evolved (Panuccio et al., 2016; Vassanelli and Mahmud, 2016). Nowadays, intense research on neurobiohybrid systems is conducted all over the world, with the objective to provide new tools for replacing or restoring impaired neuronal functions, or even enhance physiological brain function. However, such therapeutic strategies need to be established on neural implants ensuring a bidirectional communication with living neuronal cells (Broccard et al., 2017; Buccelli et al., 2019).

### **OBJECTIVE OF THE TEAM** within the Institute for Electronics, Microelectronics and Nanotechnologies (IEMN, Villeneuve-d'Ascq, France)

In this context, our team aims to develop an implantable neurobiohybrid system, which could be used *in vivo* as a biosensor and neuronal prosthesis. For this purpose, the neurobiohybrid system should include artificial neurons capable of self-learning, able to adapt in real-time to the biological variations of brain neurons (which requires a bidirectional communication between the brain and the system) and functioning with only analog signals to avoid analog to digital and vice-versa conversions (Serruya, 2017; George et al., 2020). Such an artificial neuron has been developed and characterized within our laboratory. This artificial neuron was created in 65nm TSMC CMOS technology and generates biomimetic signals with an amplitude and a temporal resolution of the spikes mimicking those of living neurons (~ 100 mV and 1 to 2 ms). Due to their very small dimensions and their low energy consumption, they are very good candidates for designing a new generation of implantable neurobiohybrids of high therapeutic value. These artificial neurons have been patented (FR20160053175) (Sourikopoulos et al., 2017). Our current objective is to demonstrate a bidirectional communication between these artificial neurons and living neurons.

### PREVIOUS RESULTS

Previous work using PC12 cells differentiated into catecholaminergic neurons after 14 days of exposure to nerve growth factor (NGF) enabled the team to demonstrate the actual stimulation of

neuronal cells using a neuromorphic signal similar to the one generated from artificial neurons (Henniquau, 2021). The cells were grown onto gold microelectrode arrays designed in our laboratory and coated with poly-D-lysine and collagen to promote cell adhesion to the devices. The array was composed of 5 cm gold lines on a glass substrate. Electrical stimulation through the lines was confirmed by calcium imaging, therefore achieving the proof of concept of a unidirectional communication between artificial neurons and living neuronal cells.

## **THESIS WORK**

In this context, my thesis project aims to demonstrate the bidirectional communication between biological neurons and artificial neurons. To reach this goal, I will pursue the following objectives: 1- improve the interfacing between artificial and living neurons by investigating more specifically the question of the attachment and location of living cells onto the neurobiohybrids, 2- further characterize and establish this bidirectional communication between artificial neurons and biological neurons by recording the subsequent response of the neurons to the biomimetic signal by electrophysiology and/or by using an action potential probe, and 3- demonstrate the ability of biological neurons to activate a network of artificial neurons, and vice-versa, in order to establish the bidirectional communication within such new neurobiohybrid interfaces.

## **CURRENT ACHIEVEMENTS**

Until now, my work has focused on the first objective: a better interfacing of the neurobiohybrid device and the cultured living neurons. At this stage of our work, several patterns of gold micro electrode arrays have been designed and their interactions with living neurons will be studied. In parallel, we plan to improve the coatings of these arrays, in order to obtain a more reliable interface between the electronic devices and the living neurons.

In parallel, and in line with the second and third above-mentioned objectives, in order to electrically stimulate and record individual cellular activity simultaneously, we designed a complete electronic bench including calcium imaging to correlate biological events with electrically-recorded events. The stimulation of living neurons is carried out with a generator sending the biomimetic signal. Ultimately, the artificial neurons will be implemented in the setup to establish a fully analogical communication loop between them and the living neurons. This in-house bench represents the first step needed to reach the main objective of my thesis and establish a bidirectional communication between living neurons and artificial neurons. In parallel of the development of this recording bench, the design of specific “recording” neurobiohybrids has to be improved to obtain a better signal-to-noise ratio.

Last, other neuronal cell types including mouse primary cultures of neuronal origin and human-derived neurons will be used to further confirm the bidirectional communication loop between artificial and living neurons. Ultimately, the selected neurobiohybrids should be tested in organotypic cultures and brain organoids, which provide three-dimensional environments closer to the actual conditions of the target organ (ie. the brain).

## **CONCLUSION**

In conclusion, my work will pave the way for the development of a new generation of intelligent implantable medical devices. This ultimate goal requires to work on the power supply of such neural implants although our solution is highly energy-efficient (only 4fJ/spike which improves prior state-of-the art by 2 or 3 orders of magnitude (Sourikopoulos et al., 2017)). The flexibility of the neural implant needs also to be enhanced in order to develop a fully biocompatible neurobiohybrid implant with major medical indications such as neurodegenerative diseases or age-linked macular degeneration.

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