Abstract

The brain is an extremely complex organ whose exploration and understanding requires the use of several different *in vivo* approaches at multiple spatial and temporal ranges; one such approach, developed in the last decades, aims at understanding how neural networks with thousands of neurons process and generate signals at the single neuron and single neural event levels by combining electrical readouts and optical stimulation. However, one major challenge is the creation of devices that enable the implementation of these methods to a high number of neurons in living brain tissue with high precision and accuracy and with minimal tissue damage.

To this end, neurotechnologies represent a great example of the merging of different disciplines, such as microtechnologies and electronics to realize real-world devices able to extract meaningful neuroscientific data. One type of device is the Michigan neural probe, which consist of micrometric sized silicon (or polymeric) cantilever tips (typically 1 to 10 mm long, 100 µm wide, 25 µm thick) embedding micro-scale sensors (such as microelectrodes) for neural activity readout and/or actuators (such as microlight emitting diodes or microwaveguides) for neural activity photostimulation.

While these micrometric scale devices are appropriate for interfacing with neural networks with single to few neuron resolutions, their coupling with microscale sensors and actuators limits their functionality, preventing them from studying neural populations with high degrees of accuracy and functionality. Examples of such limitations include device bulkiness; lack of simultaneous integration of sensors and stimulation sites in high numbers; limited optical functionality – generally allowing for the illumination of the entire population, or localized illumination of parts of the network, through integration of several light-emitting diode sources, but resulting in excessive heat generation.

To tackle these challenges, which are associated with the use of sensors and stimulation sites based on microtechnologies, we develop and integrate nanotechnologies in minimally perturbative neural probes for simultaneous neural network readout and selective activation and deactivation of neurons. As a first example of nano-circuit integration on microprobes, we validate the use of nanophotonics based on add-drop ring resonators to shine light in the area(s) of interest without any heat generation and resulting in the photoactivation of the desired

neurons. Remarkably, these nanophotonics allow for both reducing our device dimensions due to their small footprint and for integrating an arbitrary number of stimulation sites without any significant increase in the device's lateral dimensions. Besides, we demonstrate their use for multi-color illumination, which can be used to stimulate either different types of neurons in the brain or to access different functions (such as activation or inhibition of neural activity). A second example of integration of nanotechnologies in microprobes is the fabrication of chirped nanogrooves to focus the output light to either illuminate single neurons or spread light more efficiently; a final example is the integration of carbon-based nanomaterials on sensing microelectrodes in an effort to improve the microsensor-neuron interface.

This work describes the design, simulation, fabrication, characterization, and *in vivo* validation of these microscale devices integrating nanoscale circuitry and components. We first give an overview of the brain's networks, connectivity and functionality (page 4) of neuroscience methods that measure and manipulate brain activity (page 9), and of state of the art microinvasive tools for high resolution neural networks studies (page 19). First, we describe the integration of nanotechnologies in microscale devices. in form of nanophotonic circuits embedding optical switches as passive on-demand demultiplexers for area selective illumination (page 45) and directional couplers for multiwavelength illumination for activation or deactivation of neurons (page 46). Their integration, along with arrays of sensors is explained in page 69. Then we illustrate the fabrication processes to realize the nanocircuits, embed them onto microscale probes, and connect them to macroscopic instrumentation (page 99) so to validate both the nanophotonic circuit's capabilities (page 106) and those of the electrical's (page 133). We explore nanoscale carbon-based materials to improve the sensors' interfaces and neural signal readout (page 137). We finally validate the nanocircuit's functionality *in vivo* by measuring both the neural activity (page 150), and the device's capability of exciting neural cells in the area(s) of interest (page 152). As such, we have proven the capability of these nanotechnologies to interface with the brain tissue in a minimally invasive way, and with high degrees of functionality and accuracy.