Technology for interacting with the brain the way the brain interacts with itself

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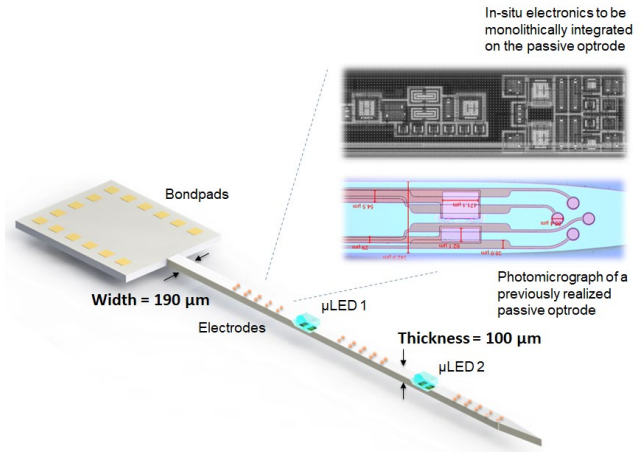
In order to better understand the brain and better treat brain disorders, it needs to be neuromodulated by means of 'brain-like' waveforms[1]. Moreover, these waveforms need to be applied in a smart way, based on feedback and in a closed-loop fashion. This requires sensing technology, not only for reading the electro-chemical signaling of the brain itself but also of other physiological parameters. Additionally, this feedback needs to be self-learning so it can learn to recognize the (personal) brain activity and connectivity characteristics that characterize a symptom and the intensity of a symptom. It then selects an optimal stimulation design to normalize the symptom by increasing or decreasing connectivity to change the network structure. Finally, it can predict symptoms to prevent relapses of chronic disease states[1].

The above needs are still far away from the state of the art. State-of-the-art neuromodulation is almost exclusively done using tonic rectangular pulses, at a single stimulation site, often not based on any form of feedback from the brain itself, and never self-learning. State-of-the-art technology for neural recording is not able to record the infraslow waves that modulate and thereby synchronize the more local brain activity, and, as it is either acquired from passive electrode arrays or from CMOS-based probes, is not able to reveal the brain's small-world emergent network behavior[2].

Innovative technology for both neuroscience (leading to a better understanding of the brain) and neuromodulation (leading to better treatment of brain disorders) should thus: 1. cover large parts of the brain for recording (reading) and stimulation (writing) and thus make use of flexible, stretchable arrays; 2. be minimally invasive; 3. excite or inhibit multiple neurons in various regions of the brain accurately (viz. with high spatiotemporal resolution), 4. with precisely controlled degrees of synchronicity amongst recorded or stimulated neural elements, 5. with more 'brain-like' stimulation patterns, such as noise, burst, infraslow waves, preferably using neuromorphic devices and self-learning interfaces (see figure), 6. by means of electrical, optogenetic, or other (e.g. ultrasound) neuromodulation (see figure); 7. record from, and stimulate, larger populations of neurons or assemblies than was hitherto possible; 8. do so in a 'brain-like' fashion that reduces data, but preserves information for self-learning and closed-loop control; and 9. last ideally forever, and thus be adaptive, upgradable, biocompatible, and biostable.

This talk will address how these 'bioelectronic medicines' can do this, what they will look like, and which future microfabrication and circuit and system developments are needed to make them a reality.



The layout of a microfabricated active optrode for neuroscientific research that allows for multi-site optogenetic neuromodulation and wide-bandwidth electrical recording. Credits: Ronaldo da Ponte, TU Delft. Not yet published.

1. Dirk De Ridder, Jarek Maciaczyk & Sven Vanneste. The future of neuromodulation: smart neuromodulation, *Expert Review of Medical Devices*, 2021, 18:4, 307-317, DOI: 10.1080/17434440.2021.1909470.
2. Stuart W. Hughes, Magor L. Lörincz, H. Rheinallt Parri, and Vincenzo Crunelli: Infraslow (<0.1 Hz) oscillations in thalamic relay nuclei basic mechanisms and significance to health and disease states, *Prog Brain Res*. 2011, 193:145–162. DOI: 10.1016/B978-0-444-53839-0.00010-7.