Meeting Report: NanoNeuro 2023 TCCI Report

On Thursday July 20th, 2023, the symposium NanoNeuro 2023 was hosted by the Neurotechnology Center at Columbia University and the Donostia International Physics Center in Donostia, Spain. Dr. Rafael Yuste, well known for his contributions to neural science such as pioneering the use of calcium indicators in neurons and delving into the behaviors of neuronal "ensembles" first described in the lab of Santiago Ramón y Cajal, moderated the meeting from the NeuroTechnology Center at Columbia. Meanwhile, Dr. Aitzol García-Etxarri, whose team investigates the "nano" forces at work when it comes to physics and biology, headed up the meeting from the Physics Center in Donostia. The meeting was generously sponsored by the Tianqiao and Chrissy Chen Institute, who work to support new advancements in brain science.

NanoNeuro 2023 is the 19th meeting that the NeuroTechnology Center at Columbia University has presented since it formed almost a decade ago as a response to the White House Brain Initiative by President Barack Obama, and it is the fourth NanoNeuro meeting that the center has put on. Dr. Yuste and others noted that nanoscientists created new materials (particles, probes, etc.) all the time that can be applied to neuroscience method, and it is in our best interest to meet and work together to "develop new ways to measure or change signals in the nervous system," as Dr. Yuste said.

NanoNeuro is a unique sort of conference – it features talks from scientists who have made significant advances in either nanoscience or neuroscience, and often both. Much like a many-sided die, these widely-varying perspectives offer new and exciting ways to conceptualize the infinitesimally small interactions in the brain that neuroscience is interested in looking at. Eight scientists from around the world gathered on Zoom for a day of fascinating debate watched by hundreds of attendees.

Jinwoo Cheon of Yonsei University began the series with a talk titled *A high-performance magnetogenetics, m-Torquer, for long-range and wireless neuromodulations in freely moving*

animals. Dr. Cheon explained that magnetism was an intensely valuable method for vision – such as humans using MRI, or some animals using magnetoreception to migrate. Light, magnetism, and biology worked together shrewdly to reveal unseen signals. Dr. Cheon noted that magnetic fields can penetrate tissue deeply with no interference with tissue. Unlike magnetic fields, purely optical systems can't go very deep. Thus, there was an imperative to develop magnetic strategies for optical purposes.

Luckily, the brain works on a sort of nanomagnetogenics. Brain activity is triggered by ion channel gating, and so Dr. Cheon knew he could create something that could attach to an ion channel and open or close it in a key range of force. There were previous studies showing that ferritin (a protein that stores iron) could be attached to an ion channel, but a large force was needed to move this ferritin so it was unlikely it would work. As a response to this, Dr. Cheon developed m-torquer, which he describes as a "nanocompass with high magnetization and weak coercivity." M-torquer generates torque to open ion channels of neurons and is a rotating magnetic field generator, thus making it the optimal magnetic configuration to generate a large area of constant magnetic field.

This m-torquer technique can also be applied to create magnetic activation in a target neuron. With viral transfection, a mechanosensitive ion channel called piezo 1 can be encoded. These ion channels can then be attached to m-torquer. This was tested in the mouse motor cortex to see if motor cortex stimulation of m-torquer could enhance mouse motility. These tests were successful – an experimenter could make a mouse move around left or right depending on which contralateral hemisphere was stimulated.

In the future, this technology could be used to create wireless control of social behaviors using magnetism, and from a long-distance. M-torquer could even be engineered for molecular and cellular specificity. Nothing like this has been possible with the current tools neuroscientists have at hand.

Dr. Shigeki Kiyonaka from Nagoya University followed with a talk titled *Chemical approaches for understanding physiological roles of glutamate receptors in neurons*. In this talk, he highlighted that AMPA receptors in the brain are important for synaptic plasticity, as indicated by the fact that the number of AMPA receptors is strictly regulated during synaptic plasticity. Previous methods to view AMPA's actions have been fraught - GFP (Green Fluorescent Protein) may disturb the dynamics of synaptic plasticity, and the large size of the antibody may block the synaptic cleft. Dr. Kiyonaka introduced a new method called Ligand-Directed Acyl Imidazole (LDAI) chemistry. This procedure makes the AMPA receptor fluoresce.

The novel technique used to accomplish this adds a TCO group to the area before adding a fluorophore.

Next, Dr. Xiaojie Duan from Peking University presented a talk discussing *Nano-enabled brain-wide neural Interfacing*. Dr. Duan began her talk by noting that network behavior involves coordinated behavior across distributed neural networks. The challenge was how to visualize this behavior. There were already several techniques to map activity across the brain, such as EEG and MEG, but these had too many limitations. Thus, Dr. Duan saw that there were to preeminent solutions. First, to develop a shape-changing electrode array for minimally invasive large scale intracranial brian activity mapping. And second, to create MRI-compatible electrodes for simultaneous deep brain stimulation and fMRI studies. The first solution would effectively produce a brain-wide ECoG recording. The advantages of this approach would be millisecond-level temporal resolution, spatial resolution to the micrometer, and high bandwidth. However, in the past, this approach would require craniotomy, which could then lead to infections and inflammatory responses. Instead, a shape-changing electrode array could be easily inserted into the brain through a small hole. It would then unfold into the field, upon which time the applicator would be removed, the whole apparatus having a mesh-like structure and a shape memory that could be thermally induced. This electrode array has been used in rats before and has been found to be minimally invasive, and the array does remain functional after the shape transformation goes into and out of the brain.

The next solution Dr. Duan explored was based on the idea that simultaneous DBS (deep brain stimulation) and fMRI would provide a structural and functional image of the whole brain. The current problem, however, was that the artifacts from electrodes implanted by DBS would prevent whole brain mapping. To combat this problem, Dr. Duan explained, scientists should change the material of the electrodes, using graphene fiber instead, and change the injection capacity to be slightly lower.

Next, Dr. Michael Krieg of ICFO gave a talk where he introduced a system called PhAST – photons as synaptic transmitters. Dr. Krieg noted that neuronal activity could be modulated through magnetic, electrical, pharmacological, and optical interventions. Thus, light sensitive neurons could be created in the brain that would respond to optical input. He explained that this was not a new idea – in fact, in 2002 a tripartite system to confer photosensitivity in hippocampal cells was created. This progress ultimately lead to the tool of channelrhodopsin, now a hugely adaptable and helpful tool in science. Dr. Krieg developed mice with photons-as-synaptic-triggers and placed them in a nociceptive avoidance circuit. Control of mouse behavior to experience or not experience pain was able to be exerted through PhAST neurons.

In the following talk, Dr. Juliet Gopinath of the University of Colorado Boulder also spoke about light. In her talk *Shedding light on the brain: super-resolution and multiphoton microscopy*, Dr. Gopinath demonstrated a method of miniature microscopy for live animal imaging. One could use stimulated emission depletion microscopy (STED), a super-resolution microscopy often used in neurology that allows scientists to resolve many small details on a neuron. This type of microscopy is often used to look at Alzheimer's-related structures. However, one could also use stimulated emission to de-excite fluorophores. With the combination of an excitation beam and a STED pattern of a slightly different wavelength, images can have a point spread function (PSF) that is much smaller, increasing resolution by several orders of magnitude.

Lisa Poulikakos of UCSD gave a very interesting talk called *Nature-inspired colorimetric metasurfaces for next generation, on-chip imaging of tissue microstructure*. Poulikakos first explained that nanophotonics was extremely useful for tissue and microstructure imaging. However, she urged, there was a pressing need for new diagnostic tools for organ fibrosis. Poulikakos has developed a new class of metasurfaces that maps tissue onto color for diagnostic processes. This work was inspired by butterfly wings, which have a strong interaction with visible light and display color change depending on their environment. As a parallel, healthy tissue and fibrotic tissue react differently to light, and will display different colors depending on the health of the tissue. Nano-optical metasurfaces can map these tissue microstructures onto normal structural color, which can then lead to a diagnostic conclusion.

Moving more to the "neuro" side of "NanoNeuro," Dr. Alvaro Pascual-Leone of Harvard University spoke about the future of noninvasive neuromodulation, a quickly growing field where researchers attempt to modulate brain activity or brain states without inserting devices into the brain. Dr. Pascual-Leone clarified that noninvasive neuromodulation does not represent a treatment for illness, but offers a framework that allows modulation to improve human life. He gave the example of combining the use of a TMS device with EEG, and guiding it with fMRI. This could produce a kind of individual brain fingerprinting. One could then take this idea and apply a precision medicine approach, leading to individualized TMS patterns – making TMS treatment high personal and ideally more effective.

Finally, Dr. Adam Cohen of Harvard University gave a keynote talk on a new electrophysiological system for understanding memory. He first noted that making a memory engages brain mechanisms across space and time. Bioelectrical dynamics, synaptic plasticity, and brain-wide gene expression come into play – all of which function on axes of time and space. A key way we look at cells creating memories is through electrophysiology, which works on the order of time and space. Dr. Cohen presented a method of structured illumination for

all-optical electrophysiology. Essentially, spikes at the soma evoke two different kinds of dendritic events, and the subthreshold voltages of these cells reflect the stimulus location. However, all of the information on where the stimulus came from disappears by the time a spike is produced. Despite this, there is still information to be found on stimulus location and spiking history. As a rule, distal dendrites need to be depolarized for about 15 ms for a back-propagating action potential to become a spike. This sustained stimulation then opens a window for dendritic spikes. Knowing this dynamic, optical tools can then be used to understand where the signal came from.

In the closing remarks, the NeuroTechnology Center and DIPC extended their deepest thanks to the Tianqiao and Chrissy Chen Institute for sponsoring this conference, and for helping to further the mission and development of sophisticated brain science.

Lux Steinberg is a Lab Manager and Research Scientist at Columbia University. She wrote this meeting report as part of the Tianqiao and Chrissy Chen Institute Science Writers Fellowship which aims to extend the conversation beyond the meeting with the hopes of sparking new ideas and collaborations.