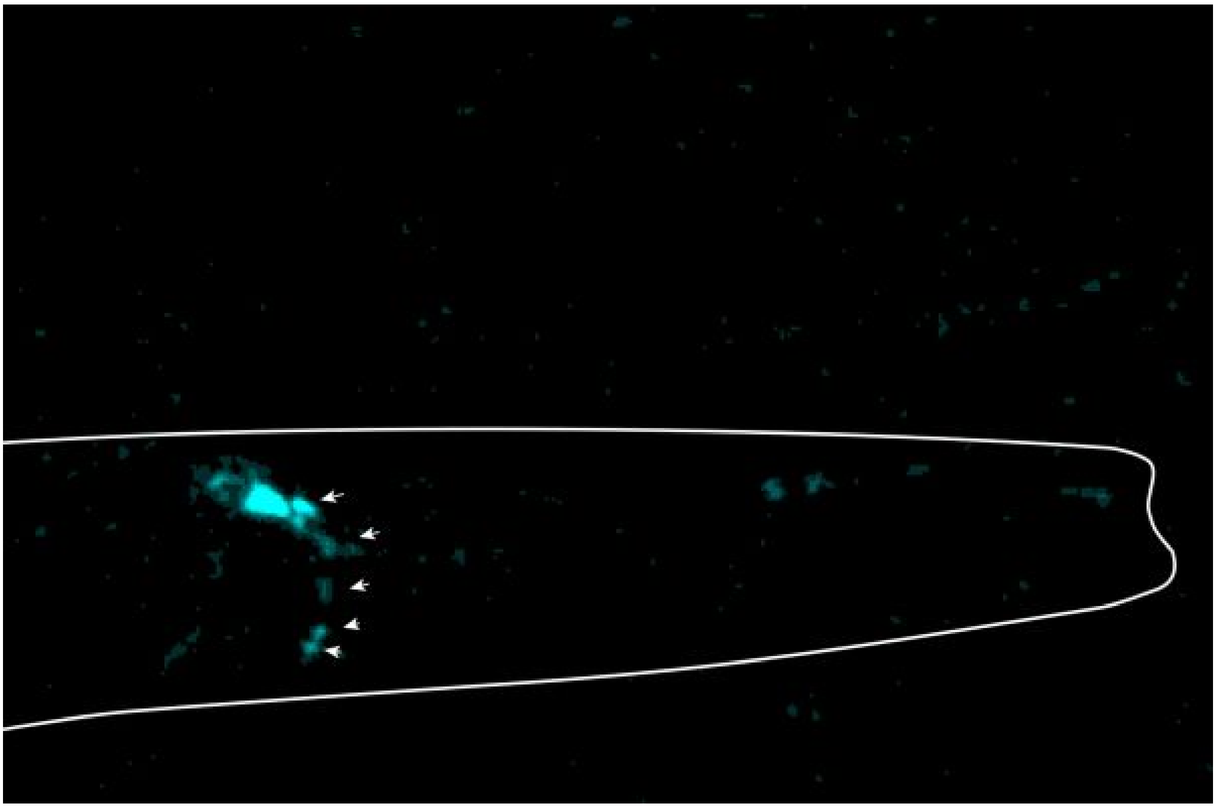

Exploring synaptic engineering's role in understanding neural circuits

Prof. at ICFO Michael Krieg, together with Prof. It ai Rabinowitch and Prof. Daniel Colon-Ramos have published in Nature Reviews Neuroscience a thorough review of synapti engineering, an emerging approach to studying neural circuits describing the current strategies and applications and sharin their visions about the future of the field.

January 08, 2024

The place where our behavior, memories and thoughts occur can be traced down to the microscopic gaps between the neurons, the synapses. In these spaces our neurons connect and communicate with their neighbors - or with those in farther regions of the brain-, by transmitting information from the sender, the presynaptic neuron, to the receiver, the postsynaptic neuron.

This transmission of signals allows the information to flow throughout the nervous system, forming complex circuits that are essential for all aspects of brain function and behavior. Understanding how synapses work and engineering new connections is crucial to decipher the complexities of brain and behavior, and to address various neurological conditions. There are several methods to manipulate and study these neural circuits, but most of them often require complex hardware, invasive interventions, and high illumination intensities, potentially leading to side effects. In this context, synaptic engineering offers an alternative by focusing on single synaptic connections between neurons, without the need for real-time external monitoring or triggering. In synaptic engineering, researchers can create synthetic synaptic connections and introduce them to already existing neural circuits or, generate new circuits. By emulating a circuit, we can learn a lot more about how it works and its plasticity, explore new connections between neurons and even establish causal relations between the structure of those circuits and how they function.

Although relatively recent, synaptic engineering has seen successful development and validation, especially in model organisms like the roundworm Caenorhabditis elegans, and increasingly in mammalian systems, proving itself as an effective method to study the structure and function of the neural circuits and explore new configurations.

An overview of synaptic engineering

Now Prof. at ICFO **Michael Krieg,** together with **Prof. Ithai Rabinowitch** from the Hebrew University of Jerusalem and **Prof. Daniel Colon-Ramos** from the Yale University School of Medicine, has published in Nature Reviews Neuroscience a thorough review of the existing synaptic engineering methods, their current applications and their visions about the future of the field. The article reviews the three main synaptic engineering strategies - electrical synapses, chemical synapses and the neuropeptides, respectively - explaining their features and describing the differences in each one's dynamics, directionality and pre and postsynaptic signals.

The first strategy addressed is the engineering of **electrical synapses**, which focuses on the channels, known as gap junctions, that allow the crossing of ions and small molecules between neurons. This also constitutes the first demonstration of synthetic neuronal engineering. In vertebrates, these channels are composed mainly of a group of proteins known as connexins. By selectively expressing these proteins, researchers can manipulate and rewire the existing connections, allowing the exploration of how the information flows along the circuits.

The second approach is the engineering of **optical synapses**, where certain light-emitting enzymes located in the presynaptic neurons, the luciferases, are involved in the activation of specific light-sensitive ion channels in the postsynaptic neurons. Two experiments, one of which was designed by ICFO researchers, have demonstrated that these optical synapses can be engineered, using light as a synthetic neurotransmitter.

The third reviewed methodology is the introduction of foreign **neuropeptides** and their corresponding receptors **for signalling**, which allows the creation of new neuronal pathways and reconfiguring those already existing, helping to understand the process of modulation in the neural circuits.

Promising potential for future applications

Future directions for synaptic engineering include expanding the engineering methods, implementing on-off switching mechanisms, and exploring multiplexing-inserting multiple independent synthetic synapses simultaneously to reconfigure neural circuits.

As the article emphasizes, synaptic engineering has a promising potential for several applications beyond constituting a useful tool to test hypotheses and address questions related to basic science. Using these methods, synthetic biology strategies could be applied to modify certain behaviors in organisms, for example, to detect and attack pathogens, or be used for treating damaged neural systems. The authors conclude by envisioning the possibility of developing large-scale synaptic engineering designs, which could contribute to a better understanding of more complex neural circuits.