Einblicke in die Forschungsarbeit

FORSCHUNGSPROJEKT

„Vernetzung“

ELISA PAVARINO

Elitestudiengang Neuroengineering

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Vernetzung

Elisa Pavarino is a student of the Elite Graduate Program “Neuroengineering” at the Technical University of Munich. As part of the program’s requirements, students carry out at least one research internship, in order to acquire valuable research experience before graduate studies. Elisa Pavarino chose to do her research internship at the Lichtman Lab at Harvard University, where she gained in-depth skills and knowledge related to connectomics, an emerging field of Neuroscience whose aim is to build the wiring diagrams of the brain.

Introduction.

The research project revolved around the study of the nerve of a mouse, both at the bundle and at the neuromuscular junction (the synapse where the peripheral nervous system makes contact with the muscle fibers). In particular, the developmental stage of interest is the one of the newborn mouse (or, more precisely, post-natal day zero). This is because at this early age, the morphological wiring of nerve components undergoes drastic changes, due to development and learning. Thus, the aim of this project was to build the connectome of the nerve of the newborn mouse nerve and to possibly understand what mechanisms can lead to the final wiring diagram in the adult mouse.

More specifically, the goals of the project were twofold:

1) At post-natal day zero, axons are maximally complex and branched, while after learning all but one branches will prune through a process called synapse elimination [1]. In this project, the Lichtman group is interested in reconstructing all the axons of the sample nerve, and investigating if there is a relationship between the branches of the different axons at each neuromuscular junction. Furthermore, they are keen on investigating whether there are some cues at post-natal day zero that indicate which branch will eventually retract.
2) At post-natal day zero, each Schwann cell (glial cells of the peripheral nervous system) enwraps multiple axons, while in adulthood, only one axon will be enwrapped by each Schwann cell. The Lichtman group interested in whether the nature of such interaction is random.

Methods

Elias Pavarino personal goal was to reconstruct an entire axon, following its branching pattern and studying how many junctions it makes. Surprisingly, only 7 neuromuscular junctions were found --- one order of magnitude less than had been hypothesized in previous studies!

While reconstructing the axon, Elisa and her supervisor Dr. Yaron Meirovitch realized that one of the possible indicators about which branch would ultimately be the survivor could be the distribution of synaptic machinery: The ideas is that axonal branches that are more dense with synaptic vesicles are more likely to win the competition against the neighboring branches. To investigate this, Elisa and her supervisor trained a neural net to classify synaptic vesicles. This is still ongoing research, as they are, at the moment, trying different variants of the network, with different classes.

In parallel to this line of research, they performed a theoretical analysis on the bundle of the nerve to address the second question mentioned above, which was to investigate the nature of the neuro-glia interaction in the peripheral nervous system at post-natal day zero.

A first hypothesis was that the Schwann cell-axon interaction could be random. A second was that perhaps the Schwann cells greedily wrap whichever axon is closer to them in space. To test their hypotheses, Elisa and Dr. Meirovitch built a graph from the connectomic data of the nerve bundle, and computed some of its properties. Then they created four different generative models for random graphs, implementing every time more compelling biological constraints, and compared the properties of the generated graphs with the ones of the biological graph. The result is that they were able to prove that the interaction between Schwann cells and axons is not random, and that distance is not a sufficient criterion through which Schwann cells ultimately choose the only axon they will wrap in adulthood.

Conclusions

This project was a milestone for the candidate's young scientific career, providing her in-depth knowledge of the peripheral nervous system, and skills in cutting-edge technologies, both of which are highly valuable qualities for future neuroengineers. The project also showcases the interdisciplinary skillset that is required in neurotechnology, requiring an understanding both of modern microscopy, connectomics and computational methods.

Elisa Pavarino wishes to thank Dr. Lichtman for hosting her in his Lab, Dr. Meirovitch for the great supervision and guidance, the Elite Master Program in Neuroengineering, together with the Elite Network of Bavaria, for the marvelous opportunity.

[1] Lichtman, Jeff W., and Howard Colman. "Synapse elimination and indelible memory." *Neuron* 25.2 (2000): 269-278.

Elite Graduate Program „Neuroengineering“:

https://www.msne.ei.tum.de/en/home/

More information:

https://lichtmanlab.fas.harvard.edu/