The Self-Assembling Brain: Contributions to Morphogenetic Engineering from a Self-Organizing Neural Network in the Insect Brain

P. Robin Hiesinger[1]

[1] Freie Universität Berlin, Germany, Königin-Luise-Str. 3, 14195 Berlin
robin.hiesinger@fu-berlin.de

Abstract

Self-organization is a fundamental principle of the development and function of living systems. Decentralized self-assembly of neurons that act as autonomous agents leads to complicated neural networks in the brain without the need of a blueprint, i.e. without endpoint information. Key principles of the self-assembly of neural networks are (1) algorithmic growth based on limited input information, (2) reliance on iterations of simple rules that often utilize stochastic dynamic processes, and (3) non-deterministic variability, yet functional robustness of the resulting network. Approaches to morphogenetic engineering of functionally robust computational networks through self-assembly may benefit from an understanding of such principles from biological systems. The extraction of such principles is dependent on our ability to observe the self-assembly of neural networks at sufficient spatiotemporal resolution in order to aid data-driven computational modeling. Here, I present quantitative 4D microscopic video data and computational modeling of the self-assembly process of a neural network with more than a million synaptic connections in the fly visual system. Based on long-term imaging we have previously extracted a set of self-assembly rules and engineered a deterministic computational model that recapitulates the network's self-organization at the cellular (autonomous agents) level. In a second step, we have now measured and modelled the underlying stochastic dynamics at subcellular levels. Our analyses indicate that stochastic dynamics of neuronal extensions are a prerequisite for flexible and robust self-assembly through algorithmic growth based on simple rules.

Neuroscience and Artifical Life Research

Artificial life research concerned with self-assembly of complex structures has in recent years progressed largely independently from neuroscience research concerned with the self-assembly of brain connectivity. Yet, self-assembly of complicated, functional neural networks represents a largely unmet challenge in artificial life research.

The self-assembly of the brain creates a remarkably robust product: a vast nerve cell network that ensures reproducible animal behavior. Yet the outcome of brain development is not completely precise: e.g. the brains of monozygotic twins are not identical (Hiesinger and Hassan, 2018). Furthermore, nerve cells, which play the role of autonomous assembly agents, show a remarkable ability to compensate for perturbation during self-assembly. Neuroscience is only beginning to uncover how the brain grows to be flexible but precise, reproducible but individual and variable but robust.

New approaches in neuroscience may help to bridge the gap with approaches in artificial life research. First, new advanced imaging technologies have enabled us to non-invasively and quantitatively observe and record both variable and robust parameters of the self-assembly process live. Second, based on these data, the development of deterministic and stochastic modeling approaches is paramount. Progress on both fronts in our study of the self-assembly of the visual information processing centers in the fly brain have reached a stage, where I regard cross-talk between the fields and direct comparisons of modeling approaches in developmental neuroscience and artificial life research highly desirable.

Self-Assembly of Brain Connectivity Live

We have developed non-invasive multiphoton live imaging of visual circuit assembly during normal brain development in a small model organism with a complex brain (Langen et al., 2015; Özel et al., 2015; Jin et al., 2018). The optic lobe in the fruit fly (Fig. 1A-B), contains ~50.000 neurons with complicated morphogenesis, including long-range 'wiring' through axons and dendrites and several million synapses.

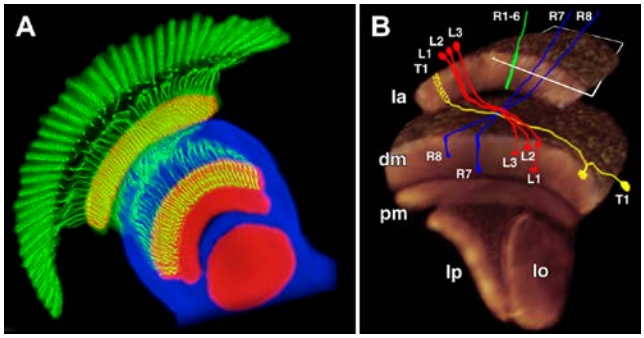

Fig. 1: The Drosophila optic lobe as a model for a self-assembling neural network. A: anatomical structure (green: photoreceptors, red: synaptic regions; blue: cell bodies). B: Selected nerve cells.

Our 4D 'video footage' includes the entire morphogenesis and self-assembly process at subcellular resolution, from axon pathfinding to the dynamic assembly of synaptic contacts. In particular, we have focused on the connectivity of photoreceptor neurons with their target cells. These include the highly precise 'synaptic ensembles' of pre- and postsynaptic neurons mapping individual points in space in

the brain according to the principle of neural superposition (R1-6 in Fig. 1B). Neural superposition is a wiring phenomenon that was central to the Tübingen school of cybernetics throughout the 60s-80s. (Kolodkin and Hiesinger, 2017; Langen et al., 2015). A second type of photoreceptor neurons carry color information and are wired in a separate region of the optic lobe (R7 and R8 in Fig. 1B). Quantitative data from the 4D analysis of the morphogenesis of the wiring diagram have guided (and placed important constraints) on subsequent computational modeling. In the case of neural superposition, we have previously presented a determinstic computational model based on three simple pattern formation rules in collaboration with the Altschuler-Wu lab at UCSF (Langen et al., 2015). This model predicts that a simple patterning process predetermines connectivity through spatiotemporal vicinity of presumptive synaptic partners at the time of synapse formation. This analysis has highlighted the algorithmic nature of information underlying the self-assembly process: rather than information specifying actual connectivity, algorithmic growth creates 'sorting' states of the system that serve as input to subsequent steps of the algorithm. Similar to concepts presented for cellular automata, surprisingly little information is required for algorithmic growth to create deterministic patterns that could not be predicted from reading the 'code' that generated them.

From Stochastic Dynamics to Robust Brain Wiring: Simple Rules of Self-Assembly

Both cellular automata and our model of neural superposition wiring discussed above are based on deterministic algorithmic growth. However, the underlying behavior of neurons that act as autonomous agents exhibits stochastic dynamics at both molecular and subcellular levels. For example, photoreceptor neuron growth cones exhibit distinct phases of stochastic filopodial exploration during the axonal sorting process (Özel et al., 2015).

Intrinsically stochastic developmental processes can lead to both variability or precision in the outcome. Synapse-specific brain wiring is achievable through molecular functions that do not only tolerate, but actively utilize stochastic dynamics (Hassan and Hiesinger, 2015). However, it has remained unclear how stochastic filopodial dynamics transition to a robustly precise number of synapses.

Neural circuit assembly requires axonal and dendritic growth followed by synapse formation between specific partners. After pathfinding, axonal growth cones transition to become terminal structures with presynaptic active zones. Stochastically extending and retracting filopodial extensions occur during both pathfinding and synapse formation (Özel et al., 2015) and are thought to facilitate interactions between pre- and post-synaptic partners (Kolodkin and Hiesinger, 2017). While filopodia may initiate synaptic contacts, synapses in turn may stabilize filopodia and direct axonal and dendritic growth according to the synaptotropic model. However, R7 growth cones (Fig. 1B) exhibit filopodial retractions after nascent synapse formation. Based on our quantitative live imaging data of R7 filopodial dynamics and synapse formation, we built a computational model based on a simple algorithm (Fig. 2):

Rule 1: stochastic filopodia initiation leads to probabilistic and reversible filopodial contact formation.

Rule 2: filopodial contacts probabilistically promote synapse formation and inhibit further filopodial initiation.

In this model synapse formation is driven by stochastic filopodial exploration and feedback-controlled by the shutdown of filopodial dynamics once a limited number of synapses has formed. This model may provide a general principle for robust synapse formation based on stochastically dynamic growth processes.

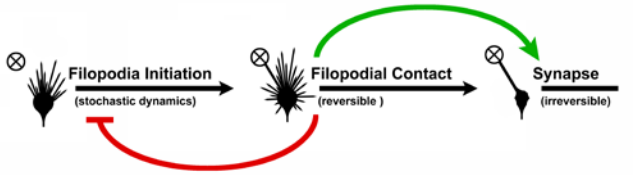

Fig. 2: A model for feedback-controlled formation of a limited number of synapses through stochastic filopodial dynamics

Our live analyses and modelling show how stochastic dynamics of neuronal extensions can become a prerequisite for flexible and robust self-assembly through algorithmic growth based on simple rules.

Based on these findings, I would like to discuss the following contributions as considerations for current algorithmic approaches in morphogenetic engineering:

1. Specific rules sets that contain sufficient information and utilize stochastic dynamics

2. Algorithmic constraints derived from evolutionary principles during development based on stochastic processes as a basis for robust selection

3. Constraints for possible outcomes: Variability, individuality and robustness

Acknowledgments. I thank Bassem Hassan, Martin Weiser, Max von Kleist and Marian Moldenhauer as well as all members of my lab for discussion. This work is supported by grants from the US-based NIH (RO1EY018884) and the Germany-based DFG (SFB958, TRR186).

References

Hassan, B.A. and Hiesinger, P.R. *(2015).* Beyond Molecular Codes: Simple Rules to Wire Complex Brains. *Cell*, 163(2):285-91.

Hiesinger, P.R. and Hassan, B.A. *(2018).* The Evolution of Variability and Robustness in Neural Development, *Trends Neurosci., in press*

Jin, E.J., Kiral, F.R., Özel, M.N., Burchardt, L.S., Osterland, M., Epstein, D., Wolfenberg, H., Prohaska, S., and Hiesinger, P.R. *(2018)* Live observation of two parallel membrane degradation pathways at axon terminals. *Curr Biol.* 28(7):1027-1038

Kolodkin, AL and Hiesinger, PR *(2017).* Wiring visual systems: common and divergent mechanisms and principles. *Curr Opin Neurobiol.* 42:128-135

Langen, M., Agi, E., Altschuler, D., Wu, L., Altschuler, S., Hiesinger, P.R. *(2015).* The Developmental Rules of Neural Superposition in *Drosophila*. *Cell*, 162(1):120-33

Özel, M.N., Langen, M., Hassan, B.A., and Hiesinger, P.R. *(2015).* Filopodial Dynamics and Growth Cone Stabilization in *Drosophila* Visual Circuit Development. *eLife*, e10721.