Modelling collective axon growth from in vivo data reveals the importance of physical axon-axon interactions

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Résumé

Neurite extension is essential to establish complex neuronal circuits during brain development. Neurons extend their axons in a crowded environment to reach target territories and connect to specific partners. Much work has been performed on cultured isolated neurons, focusing on the response of axon growing ends to chemical guidance cues. However, the cellular mechanisms involved in the growth of axon groups in their natural environment (the brain), are still poorly understood. Our objective is to shed light on collective axon growth and branching processes in a complex environment, considering axon-axon mechanical interactions. To do so, we propose a simple mathematical model for axonal elongation that we simulate embedded in a realistic environment.
Drosophila mushroom body gamma neurons are a good biological model for collective axon growth, as their adult axonal processes grow synchronously, in a relatively short time scale and in a constraint environment (the medial lobe). Our database consists of 3D confocal images of a single Gamma neuron in its specific mushroom body, each one from a different individual. We segmented the images to extract the geometry of each neuron and normalized them to artificially place them in the same medial lobe.

To model neuron growth, each 3D step of the axon tip is determined dynamically, by a Gaussian Markov chain with two main parameters, accounting for axon stiffness and attraction to the target field. The parameter values are estimated from the axons in our data. The attractive external field is estimated for a simplified geometry of the medial lobe. We simulate the growth of every neuron in the Gamma population (650 individuals) in parallel, inside a reconstruction of the medial lobe. Axon-axon interactions are considered via volume exclusion (repulsive interactions) and neurons are not allowed to trespass the medial lobe limits. If any of these interactions occurs, the axon stops and tries to elongate in another direction until it finds a free way, losing time respect to another one that encountered no difficulty.
We find out that reaching the target in a population context is not trivial when considering mechanical interactions, suggesting that other mechanisms may be involved to accomplish

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full elongation. We show that the formation of long terminal branches is useful for this purpose. More importantly, we find out that branch formation upon mechanical interactions optimizes the effectiveness of this mechanism. Our model also predicts the particular phenotype of a mutation affecting branching and elongation. Finally, we investigate the importance of neuron stiffness and source attractiveness to achieve full elongation as well as to assure biological shape diversity.