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

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Neurite extension is essential to establish complex neuronal circuits during brain development. In particular, neurons extend long cytoplasmic projections, the 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 physical environment (here, the brain), are still poorly understood. Our objective is to shed light on collective axon growth and branching processes in a complex environment, with the help of mathematical modeling.

To study these mechanisms in the context of a living organism, we use *Drosophila* mushroom body gamma neurons as a paradigm. This population of neurons represents a good model for collective axon growth, as their adult axonal processes grow synchronously, in a relatively short time scale (around 15-20 hours), in a constraint environment (i.e. medial lobe of the Mushroom body inside the central brain). To feed our mathematical model we use an average pattern of medial lobe obtained from biological samples, and a database composed of confocal images of individual wild-type and mutants gamma neurons labeled with GFP.

Growth of individual axons is modeled by a Gaussian Markov chain in a 3D space, which depends on two main parameters estimated from real data: i- axon rigidity and ii- attraction to the target field. Furthermore, we hypothesize that axon tips pause when encountering a mechanical obstacle (i.e. other neurons or the lobe limits), and associate this behavior with the birth of long terminal branches. We show that the proposed mechanistic branch generation process is plausible. More importantly, our model predicts that branch formation in response to mechanical interactions enhances the probability that axons reach their final destination at the population level, and that axon density influences arborization patterns. Indeed, about 40% of simulated axons do not grow properly in the absence of branching in a wild-type environment, a result that is validated by biological data obtained with mutant neurons, in which axon growth defects are associated with defective branching.

To further validate the model hypotheses concerning branch formation, we are currently collecting and analyzing live-imaging data sets from brains with GFP-labeled growing axons.

We hope that combining cell biology, imaging and mathematical modeling will help us better understand the process of axon growth at the population level, in both normal and pathological contexts.