
Mechanisms of Axonal Gradient Detection
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Correct brain function requires correct brain wiring. An important step in the establishment of appropriate connectivity is the guidance of axons over long distances in the developing brain to find their correct targets. A crucial type of guidance cue axons use is concentration gradients of attractive or repellent factors. Over the past decade many new molecules have been discovered that guide axons in this way. However, as yet we still have very little understanding of the precise mechanisms by which axons detect and respond to concentration gradients. The goal of this project was to develop a mechanistic understanding of axonal behavior in gradients by building computational models of gradient detection and directed movement for axons, directly constrained by data from a novel quantitative chemotaxis assay. This assay allows relatively stable molecular gradients of precisely controlled shape to be established in a collagen gel. Using this assay we have now shown that axons can detect a concentration of only about 1 molecule across their spatial extent, making them some of the most sensitive devices for detecting gradients yet known. Our modeling work has focused on how axons can detect such small gradients given the inevitable stochastic noise in the receptor binding process. By employing spatial and temporal averaging of receptor binding signals in the models we have been able to closely match our experimental data. This leads to predictions regarding the spatial and temporal scales over which the intracellular signaling networks mediating chemotaxis operate.

Publications

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