

Quantitative and Computational Analysis of Molecular Gradient Detection by Axons**Urbach, J.S.¹, Rosoff, W.J.², Esrick, M.A.¹, Gu, M.³, Richards, L.J.⁴, Goodhill, G.J.²****¹Department of Physics, Georgetown University, Washington, DC, USA; ²Department of Neuroscience, Georgetown University Medical Center, Washington, DC, USA; ³Computation and Neural Systems, California Institute of Technology, Pasadena, CA, USA; ⁴Department of Anatomy and Neurobiology, and The Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD, USA**

An important step in the establishment of appropriate connectivity between neurons in the developing brain is the guidance of axons over long distances. 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 little understanding of the precise mechanisms by which axons detect and respond to molecular concentration gradients.

Our goals are to (1) develop a mechanistic understanding of axonal behavior in gradients by building computational models of gradient detection and directed movement for axons, and (2) validate these models experimentally using a new biomedical engineering technology we have developed that allows precisely controlled molecular gradients to be established in collagen gels.

So far we have shown using our new technology that axons are extraordinarily sensitive to molecular gradients: the most sensitive gradient detectors yet discovered in nature. In addition we have shown computationally that relatively simple mechanisms are sufficient to generate realistic trajectories for both the short term response of axons to steep gradients and the long term response of axons to shallow gradients. Our computational model makes predictions for axonal response to attractive and repulsive gradients of different concentrations and steepness, the size of the intracellular amplification of the gradient signal, and the differences in intracellular signaling required for repulsive versus attractive turning. We are currently testing these predictions experimentally.

Supported by R01 NS046059 and the Whitaker Foundation.