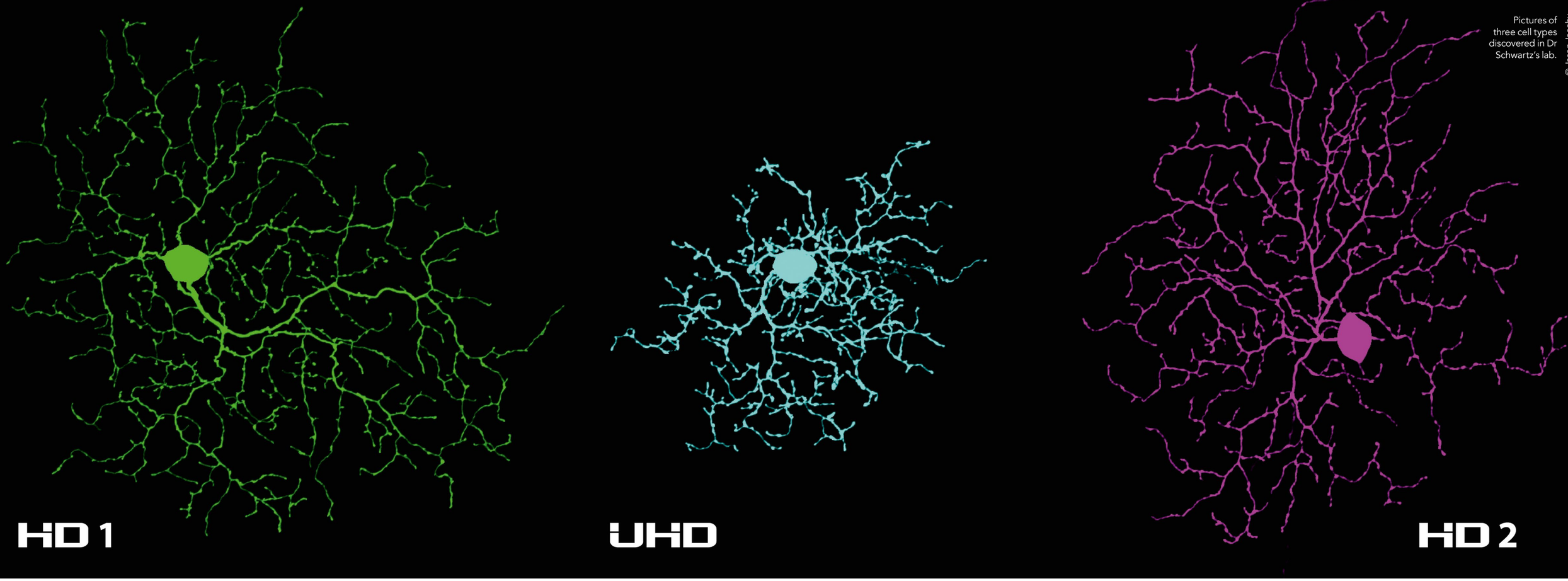


Pictures of three cell types discovered in Dr Schwartz's lab.

Pioneering novel techniques in neuroscience

Dr Gregory Schwartz of Northwestern University at Chicago, Illinois, is revolutionising the techniques used by neuroscientists. His work introduces new approaches for classifying neurons, understanding synaptic connections and modelling input-output relationships. This research uses the early visual system of mice as a model system to study multiple cell types in a single circuit and could lead to better understanding and treatment of neurological diseases.

One of the biggest challenges of contemporary neuroscience is to create a neural map of the human brain allowing for better understanding and consequently treatment of neurological diseases. Unfortunately, progress is hampered by a current inability to integrate the multiple methods of mapping and understanding neurons. Dr Gregory Schwartz utilises a mouse model to explore a unique method of amalgamating existing techniques to better understand the diverse features of a neuronal circuit.

NEURAL CLASSIFICATION

Neural structures are diverse and often complex so classifying each type of neuron presents researchers with challenges as to the best criteria to use. Currently, five different classification methods are used; location in the brain, electrical properties, anatomical structure, the genes they express and how they connect to other neurons. It is rare for all five properties to be measured in the same neurons resulting in conflicting definitions of neuron types amongst different teams of researchers. Dr Schwartz has managed to overcome this obstacle by combining all five types of classification within a single system. The model system he has chosen is the early visual system of a mouse. Specifically, his research utilises the Retinal Ganglion Cells (RGCs) – neurons which act as the sole output of visual information from the eye to the brain.

Even within the class of RGCs, there have been several attempts at classification, without consensus. Previous criteria for RGCs have included morphological structure, functional characteristics, or molecular cues. Dr Schwartz will be the first to systematically combine all sources of information across cell types. So far, 40 different types of RGCs have been identified by the Schwartz lab and work is on-going to produce an unambiguous "parts list" of the retina.

Dr Schwartz describes his alternative method for modelling input-output relationships as a radically different, 'bottom-up' approach

SYNAPTIC CONNECTIONS

The complexity of the synapses within the retina means that many of the connections remain unmapped. Dr Schwartz has proposed a new combination of techniques to map synaptic connectivity between genetically and functionally identified cell types in the retina.

For excitatory circuits, he uses a triple fluorescent labelling strategy: putative presynaptic cells are labelled in one colour, a target RGC is labelled in a second colour, and the precise locations of excitatory synapses on the RGC are labelled in a third colour. Apposition of presynaptic and postsynaptic membranes, along with the specific excitatory synapse marker allows him to identify each synapse on the cell. For inhibitory circuits, Dr Schwartz relies on transgenic mouse lines to target particular inhibitory cells and RGCs for paired electrophysiological recordings, a

direct measure of functional connectivity. By combining his knowledge of cell function with his knowledge of cell anatomy, Dr Schwartz brings large scale connectivity measurements within reach.

THE UNIQUE GENETIC CODE OF EACH RGC

Dr Schwartz also seeks to discover the patterns of gene expression that make each RGC unique. He hopes to achieve this using another novel combination of techniques. His method of using single-cell transcriptomics alongside functional measurements has already led to better understanding of the properties of several types of RGCs. The ability of Dr Schwartz and his team to develop and apply multiple combinations of techniques in novel ways continues to advance the field of retinal neuroscience.

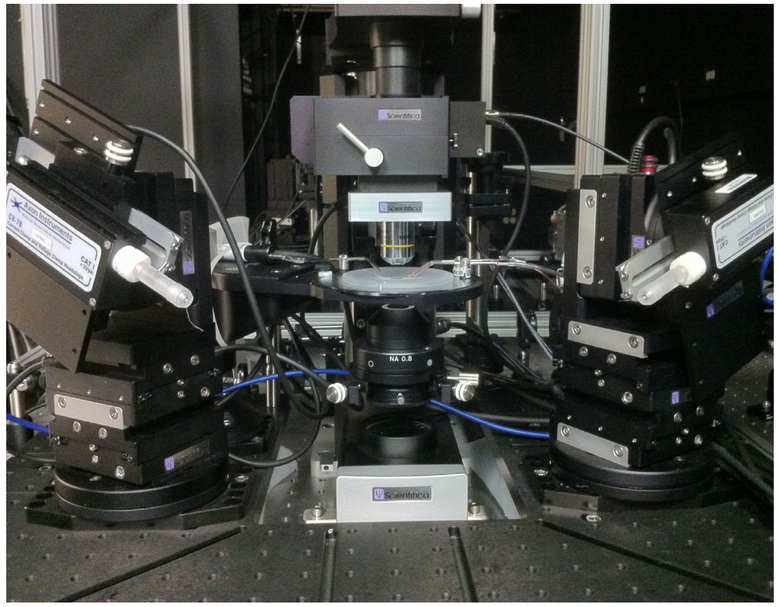
INPUT-OUTPUT MODELS

Understanding how a sensory neuron selectively responds to a stimulus is one of the key components in understanding the relationship between the input, light, and the output, behaviour. At present, artificial light stimuli are presented to the retina and outputs are described in a linear format without considering the complexity and computational abilities of the retinal interneurons. This method prevents accurate predictions of retinal reactions to natural light stimuli.

Dr Schwartz describes his alternative method for modelling input-output relationships as "a radically different, 'bottom-up' approach." A model will be built from the ground up, beginning by understanding the receptive fields of the presynaptic cells, which are then tested using thousands of artificial and natural light stimuli. By then measuring the signal processing steps at each stage of the circuit, Dr Schwartz will be able to assemble a computational model of entire retinal circuits. This modelling approach will help Dr Schwartz to understand the selectivity of the responses and therefore enable him to make predictions about the response an RGC is likely to have to a set of light patterns.

WHAT ARE THE CONSEQUENCES?

Within the field of retinal neuroscience, the integration of multiple types of measurement will allow for the definition of RGC types with "unprecedented precision". The broad nature of this work will also allow for gaps to be filled in understanding the interaction between the anatomical



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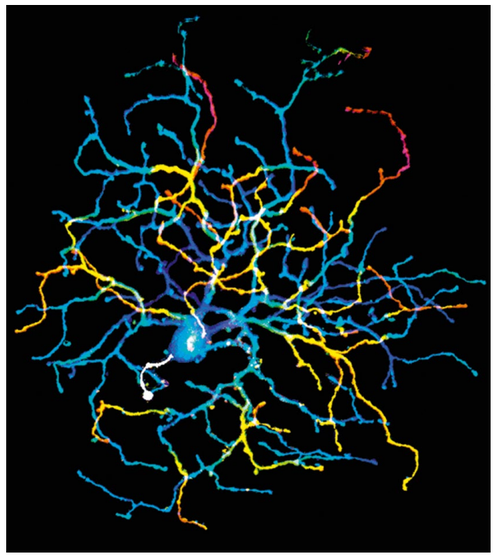
Above: One of the electrophysiology rigs in the Schwartz lab, used to record the electrical activity of retinal neurons.



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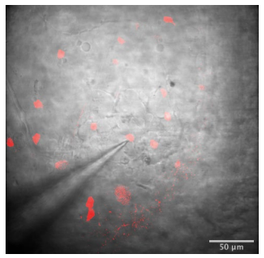

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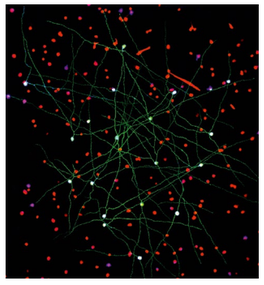

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Left: A cell type discovered in the Schwartz lab called the "ON delayed RGC." Its dendrites are coloured by depth.
Top Right: An electrode targeting a fluorescently labelled RGC under two-photon illumination.
Bottom Right: A network of electrically coupled cells in the retina (green). Cells were targeted for recording in a transgenic mouse line with a subset of cells labelled in red.

The integration of multiple types of measurement will allow for the definition of RGC types with unprecedented precision

Q&A

Which of your findings was the most surprising?

I am constantly surprised by the specificity of retinal computation. Animals have evolved cell types for particular kinds of tasks, and they are remarkably robust for those tasks. A direction selective cell will respond to movement in only one direction regardless of speed, contrast, or size of the moving object. Orientation-selective cells align perfectly to the horizontal and vertical axes of visual space. We even discovered a cell that may report whether the image on your retina is in focus.

Which of the new techniques you have developed excites you the most?

I am most excited by the prospect of combining my expertise on the functional classification of neurons with state-of-the-art single-cell transcriptomics. Often these techniques are performed in isolation in different labs, but bringing them together on the very same cells will allow us to answer questions that neither technique could alone. It is a real joy to come to work feeling like I am cracking the genetic code of the retina.

What is unique about your working environment that has allowed you to develop such radically different approaches to neuroscience?

The neuroscience community at Northwestern is enormous, high-powered, and diverse, comprising over 150 faculty members. We seem to have an expert on each technique, system, and different level of analysis. This community has given me the courage to expand my research beyond my own experimental training in electrophysiology. In particular, my foray into genetics would not have been possible without the collaboration of Dr Segal at the University of Chicago as well as a number of local researchers with whom I have frequent discussions.

How do you expect other researchers will receive your techniques?

Open and efficient dissemination of my techniques and discoveries is absolutely critical. I view part of my role in the field as unifying conflicting cell classification schemes so that researchers around the world can know for certain that they are studying the same, well-defined cell types. It will take many more people than my lab alone to complete the circuit map of the retina.

What is your biggest ambition for the future of your work?

I want to make the mouse retina the premier model for circuit mapping in the central nervous system. One day I want to be able to tell you what visual information is carried by each of the 40 different RGC types, how that computation happens in the retina, and where that information is used in the brain to influence behaviour. I hope that this degree of precision and completeness in understanding will become the standard in systems neuroscience.

Dr Schwartz also seeks to discover the patterns of gene expression that make each RGC unique

structure and synaptic properties of individual neurons as well as the properties of full circuits.

The broader public health impacts of Dr Schwartz's research could ultimately introduce better techniques to the field of neuroscience, thus not only transforming the understanding of the early visual system but also providing a toolkit for conquering the challenges of neuronal diversity in other parts of the brain. Once it is well understood how neuronal circuits function when all components are healthy, it can be better understood what happens in incidences of neurological disease.

Detail

RESEARCH OBJECTIVES

Dr Schwartz's research project aims to improve our understanding of the neural circuits of the retina by linking detailed wiring maps with functional measurements from the same cells. Several new brain-mapping techniques developed as part of the project will have broad impacts on other mapping efforts throughout the brain.

FUNDING

NIH

COLLABORATORS

Collaborator on genetics (single-cell RNA sequencing): Jeremy Segal, MD/PhD, University of Chicago
Prof Gregory Schwartz's lab:
Susan Wohlgenant, Manager
Postdocs: Adam Mani, Jason Jacoby, Jared Levine, Jillian Goetz
Graduate students: Amurta Nath, David Swygart, Sam Cooler, Sophia Wienbar

BIO

Dr Schwartz received a BS/MS in Neuroscience and a BA in Computer Science from Brandeis University in 2003. He began studying visual processing in the retina during his graduate work in the laboratory of Michael J. Berry at Princeton University where he received his PhD in 2008. Dr Schwartz continued studying the retina as a post-doc in the laboratory of Fred Rieke at the University of Washington where he also collaborated closely with Rachel Wong. Dr Schwartz has been an Assistant Professor in the departments of Ophthalmology and Physiology and Northwestern University since 2013.

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