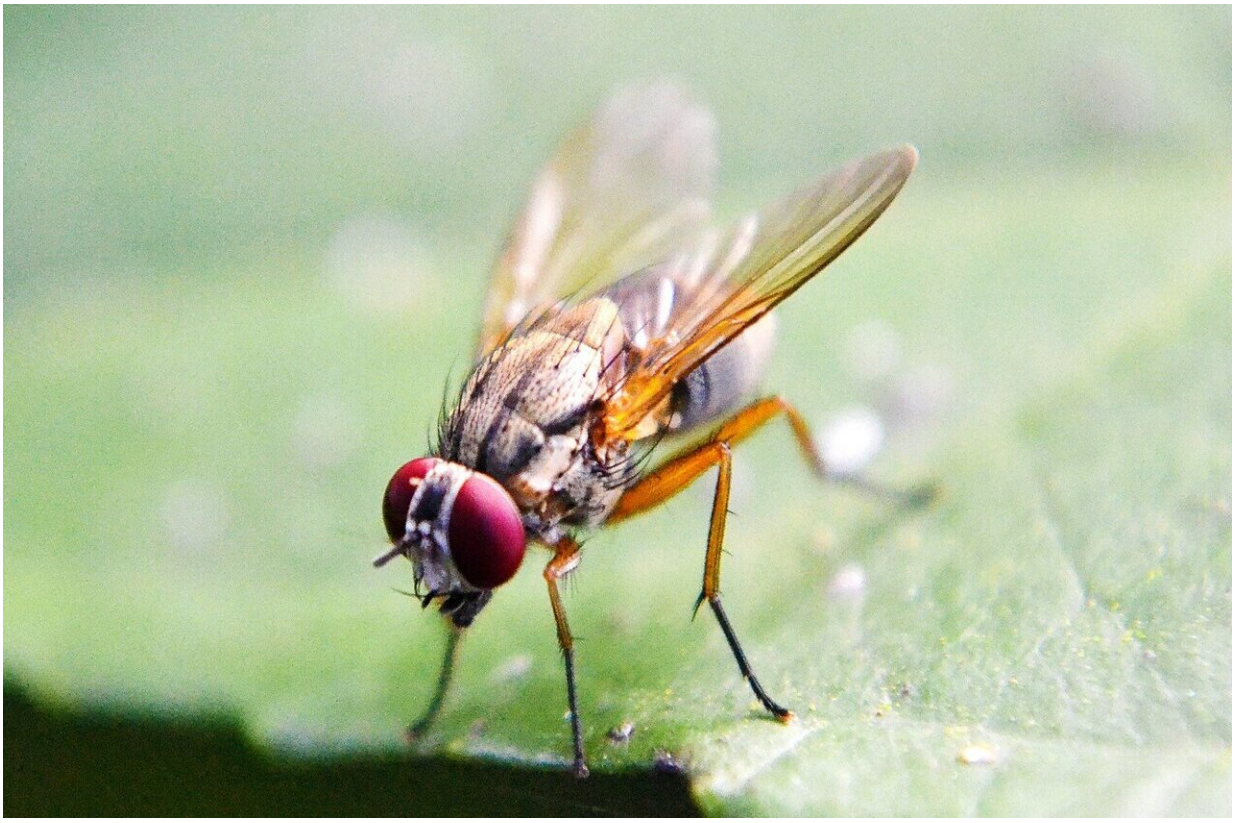
How flies develop sight: Scientists use single-cell sequencing to identify cell types in the visual system

July 31 2023



Credit: CC0 Public Domain

New York University researchers have discovered new cell types in the visual system of flies, made possible by their creation of a tool that finds

and labels neurons during development.

The study, published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), combines single-cell sequencing data with a novel algorithm to identify pairs of genes that point to previously unknown cells in the brains of fruit flies.

Fruit flies (also known as Drosophila) have long been used as a model organism to study fundamental questions about the development and function of the brain. Instead of the 86 billion neurons found in humans, fruit flies have about 100,000 neurons—making research into the brain a more manageable, yet still complex, endeavor.

The use of genetic tools that can distinguish different types of cells in fruit flies has revolutionized the study of neural circuits in the brain, allowing scientists to understand circuit development, function, and behavior in a precise manner.

"A hallmark of the central nervous system is the diversity of different cell types that are responsible for so many different functions," said Claude Desplan, Silver Professor of Biology and Neural Science at NYU and the study's senior author.

Previous research in Desplan's lab used single-cell sequencing to determine that there are approximately 200 cell types in the developing fly's visual system. Single-cell sequencing reveals gene expression, so when cells have the same gene expression patterns, they are likely doing the same job and are therefore the same cell type.

Scientists could identify roughly half of the 200 cell types in the developing fly's visual system based on their gene expression and prior studies, but they lacked a way to more easily study and label the other 100 cell types. Existing tools that allowed precise manipulation of neural

circuits of adult fruit flies often failed to label the same neurons during development, rendering these tools unfit to study cells in the developing brain.

"Moreover, the previous approach to identifying cell types involves laborious testing of numerous gene candidate combinations. We knew we needed a much more efficient approach to label specific cell types, and were able to tap into the growing amount of single-cell sequencing data that is available," said Yu-Chieh David Chen, a postdoctoral associate in NYU's Department of Biology and the study's first author.

Chen and his colleagues created a tool that takes advantage of the extensive single-cell sequencing data for the developing fly visual system to identify genes—and combinations of genes—that are exclusively expressed in certain cell types.

To find a cell type, researchers typically look for genetic markers, or single genes that are specific to a cell type. But often a gene will be expressed in multiple cell types, making it difficult to use one gene to differentiate between them. The tool the NYU researchers developed uses a slightly different approach: finding two genes that overlap only in one cell type.

By feeding single-cell RNA sequencing data into an algorithm they created, the researchers systematically identified pairs of genes that are uniquely expressed in the majority of cell types in the fruit fly's visual system at multiple stages of development. One such gene pair led to the discovery of MeSps, a brand-new cell type.

"Despite a long history of studying the fruit fly's visual system, we had never seen this cell type before," said Chen.

While future research will delve into the development and function of

MeSps—for instance, whether it detects color, motion, or other features of light—this avenue of research will be made possible by the new tools.

The researchers note that their tools can also be used to study other systems beyond vision in the developing fly, as long as single-cell data are available. Moreover, their logic of finding marker gene pairs instead of one single marker gene can be applied in research in other species.

"Instead of looking for a single good marker gene, a simple tweak of just looking at two genes can achieve high cell-type specificity," said Chen.

"This pioneering and efficient approach provides exceptional tools for the field of neuroscience to investigate developmental questions with high precision," said Desplan.

In addition to Chen and Desplan, study authors include Yen-Chung Chen, Raghuvanshi Rajesh, and undergraduate students Nathalie Shoji and Maisha Jacy of NYU; Haluk Lacin of University of Missouri-Kansas City; and Ted Erclik of the University of Toronto-Mississauga.

More information: Chen, Yu-Chieh David et al, Using single-cell RNA sequencing to generate predictive cell-type-specific split-GAL4 reagents throughout development, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2307451120

Provided by New York University