Connecting the Dots: To Read the Mind of a Fruit Fly

by Max Andersson

The common fruit fly (*Drosophila melanogaster*) in the wild.

(Photo by Rickard Ignell and used with permission.)

Aeons ago, one of Earth's earliest life forms, a tiny Precambrian bacterium, navigated the vast primordial oceans, driven solely by instinct in an ocean full of decaying organic matter to feed on. Fast forward to about 500 million years ago, same place, different times, and with this much time passing comes change. The primitive life forms have evolved for an almost unimaginable time due to many changes and events over the years. One such change was a change in feeding behavior: they started feeding on each other for sustenance. This change led to the development of the early brain and nervous system due to the higher intake in nutrients and a need for keeping “an eye out” for predators wanting to eat you. Fast forward to the present moment, and you reading this text, equipped with one of the most advanced nervous systems in the history of life, (hopefully) without a care for being consumed by a predator but rather reading this for enjoyment. It is astonishing how far we have come.

The brain is, in many ways, the pinnacle of biology, the symbol of intelligence but in many cases, just a highly complex lump of fat. A mysterious part of almost all animals but still something that we as humans do not quite understand at all. How, why, and when is consciousness achieved, and how do we distinguish between just being alive and sentient life? From sponges in the oceans, which are considered living animals but lack any significant nervous system, to the human brain with its 80 billion nerve cells and over one trillion connections between them, we are considered not only alive but also sentient and intelligent. But what about the animals with brains in between the simple and the very complex? How about roundworms, which possess around 300 nerve cells, or fish, spiders or flies, which possess around 100 000 nerve cells? Where is the line drawn, how does it work, and what differentiates us from other animals?

It is quite baffling when one thinks about the complexity of our brains, not only as physical objects but also philosophically as abstract objects. How can these cells, seemingly just atoms arranged in a certain order, achieve consciousness, complex thinking and the formation of memories? And how do we even begin to grasp the vastness that is mapping the human brain and all its connections when the numbers are so great? Due to this complexity and the highly debated ethical concerns regarding working with the human brain, it is common to work on simpler organisms called model organisms.

The first animal and model organism to have its brain fully mapped is the microscopic roundworm *Caenorhabditis elegans*. This is a worm that lives in the soil just like most other roundworms, but it is only one millimeter in length. With its low count of exactly 302 nerve cells, researchers could manually identify and assign a unique name, characteristic location, and shape to every nerve cell in its nervous system, details of which can be found here. A huge feat for its time, but by today's standards, this earlier work in neuroscience is no longer as impressive. Come 2024, the second animal and model organism to ever have its brain fully mapped is an animal you probably know very well, the common fruit fly – also known by its scientific name *Drosophila melanogaster*, which will be the main focus for the remainder of this article.

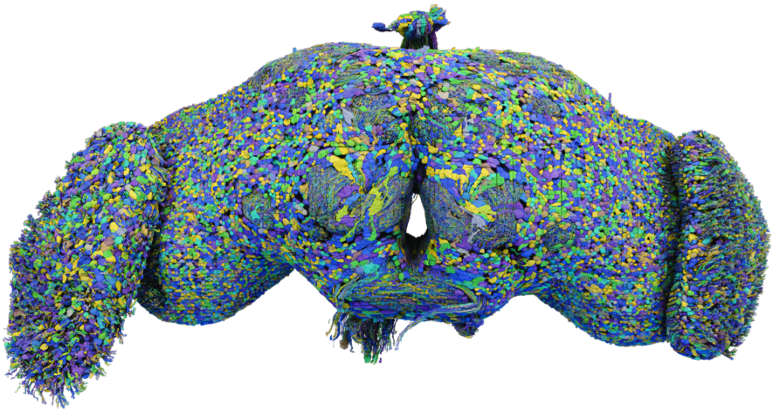
Research is often done on model organisms because it is easier in many regards, but they should also share some traits with humans. For example, sixty percent of all the genes in the fruit fly genome are also found in the human genome – and three out of four human genetic diseases have a similar version in fruit flies. On top of this, many behaviors are similar between fruit flies and human – just like us, they can get drunk, stay awake with the help of caffeine and they even serenade their love interests. In one sense, fruit flies are very similar to us and they are always around somewhere. This and much more makes them the perfect subject for research linked to humans and has made them known as "the human commensal" , which in essence means that they are the roommate who gets to enjoy the benefits of living with you (but that we sometimes do a bit of experimenting on).

The fruit fly is quite a marvelous little insect and has gone through a lot during its time as a model organism for human research. Most of us know it as a little annoyance that emerges when late summer comes around and you have forgotten to take out the organic trash or left that very ripe banana on the kitchen counter. But much of today's knowledge of genetics could not have been done without this particular fly. Due to its simple, predictable and malleable biology, it is possible to use it as a vessel or medium when researching other, complex matters. It is, for example, possible to make organisms – in this case the fruit fly, have traits from other organisms, but studying the biology of the fly itself has ultimately taught us much about biology in general because we can apply our findings to other subjects.

Thomas Hunt Morgan was the name of an almost legendary researcher who really kickstarted the utilization of the fruit fly as a research medium. His achievements include the first noble prize where the fruit fly was the subject and he later created a group of esteemed researchers called the "Drosophilists". Hunt Morgan did research on how chromosomes are involved when we inherit DNA from our parents. After Hunt Morgans' pioneering work, there have been five more Nobel prizes involving the fruit fly. From damaging DNA with X-rays in 1946 to discovering how molecules regulate our daily rhythms, known as circadian rhythms in 2017, the fruit fly has played a crucial role in many crucial discoveries throughout the years, mainly in the field of neuroscience or studies of the brain.

One of the ultimate goals of neuroscience is to completely map the brain in terms of its nerve cells and all of the possible connections between these, which is called a *connectome*. The work to map the brain of the fruit fly officially began in 1991 with a quite rudimentary discovery of how some circuits related to vision work. In 2011, an advanced map of the brain was published showing the different regions of the brain. In 2020, a big milestone was reached: a connectome showing half of the nerve cells of the central brain with all of its connections was released. Finally, in 2023, the full connectome was realized and released in a project aptly named FlyWire, an incredible achievement after many years of research.

The FlyWire Consortium is a society of researchers who have collected all the available data, compiled it, confirmed it and made a full connectome of the fruit fly's brain. This connectome is a comprehensive map of all the nerve cells, their connections with each other, which are hosted within the fruit fly brain and nervous system, as well as how they make up the various parts of these. One can imagine and compare this to a wiring diagram in electronics like the ones found in your home or like the simple ones one did in physics class during compulsory school. This consortium has been working for many years, bringing together all the necessary parts to make up the connectome. 99 per cent of all the nerve cells have now been identified and confirmed, clocking in at 140 000 individual cells. These are divided into many thousands of classes from nerve cells telling the fly how to move, where it is in relation to landmarks, what it is smelling, and if it is warm or cold, just to name some examples.



A Rendition of the full connectome of the common fruit fly *Drosophila melanogaster*. This figure includes all of the 139 255 brain cells of an adult fruit fly. The different colors represent different classes of nerve cells, showing how vast the nerves spread and are connected. Two such nerve classes are motor nerve cells which tell which parts of the body to move and nerves involved in smelling called olfactory nerve cells, which send signals from the antenna to the brain when a smell is detected.

(Image by Tyler Sloan for FlyWire, Murthy & Seung Labs at Princeton University and used with permission.)

By building a computer model of the entire brain of the fruit fly, it makes future studies on complex interactions between nerve cells easier to understand as one can see directly how the nerve cells are connected. For example, the seemingly simple task of flying in a fly is something that seems so natural and easy because that is what we see them do all the time. But when a fly flies, it has to activate many different types of nerve cells in order to see and smell where it is going: it has to keep balance, flap its wings, fly straight, avoid threats and potentially find a target for landing. All of this activity is done by different classes of nerve cells firing and feeding muscles, tissues or other target information, all for the sake of the fly having a safe flight across the room to get to that ripe banana I mentioned before – it is a fantastic feat!

Even though we are still far away from a human connectome, it is a goal worth striving for. Researchers of connectomes are pointing towards its incredibly powerful uses when it comes to understanding the underlying causes of neurological disorders such as schizophrenia and autism. However, even though there has been a lot of research conducted on these topics, we are nowhere closer to understanding why these disorders work or happen. These researchers believe that the connectome may be the answer, looking at how the brain is wired, what parts of the brain contain more nerve cells and how this is linked to these disorders. Once we have the connectome of the human brain, we might be one leap closer to understanding the mystery of the lump of fat housing us.

Max Andersson is a second-year PhD student at the Department of Plant Protection Biology at Campus Alnarp, working in the unit of Chemical Ecology in the group of Disease vectors. His work focuses on olfaction in mosquitoes, namely the malaria and yellow fever disease vectors. In his work, he is trying to unveil what these mosquitoes can smell on a molecular level, what this means functionally and how it affects their behaviour. In his free time, he likes to ride his bike, read books and spend time in nature with his partner. He often thinks about the brain, our fleeting existence as human beings, our consciousness, and what we are doing here in this world. You can follow Max on LinkedIn.