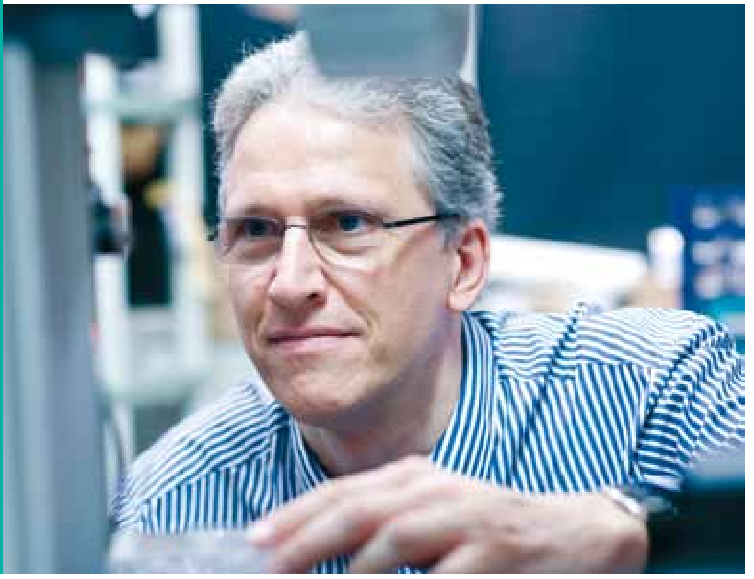


# VIRTUAL INSIGHT INTO THE ZEBRAFISH BRAIN

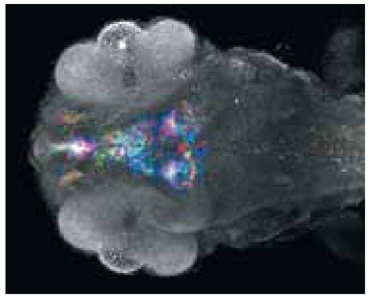
WOLFGANG DRIEVER
INTERNAL SENIOR FELLOW
SCHOOL OF LIFE SCIENCES – LIFENET

FRIAS provided Wolfgang Driever with a precious gift: the gift of time. "Over the past three and a half years I have finally been able to devote myself to matters that are simply beyond the normal research capacity of a university professor," explains the developmental biologist. "In the ordinary academic world," the Internal Senior Fellow of the School of Life Sciences – LifeNet continues, "progress is in most cases limited by your existing repertoire of methods. However, if these aren't enough to answer particular scientific questions, then it is usually impossible to pursue your research further. Developing entirely new methods is simply too time consuming." Driever's FRIAS Fellowship, however, has now given him the chance to tackle just such a project. Together with Olaf Ronneberger from the University of Freiburg's Institute of Computer Science he has developed microscopic imaging techniques and a software programme in which it is possible to view and compare all genes, and thus all the different factors that influence nerve cells, in a virtual 3D model of the zebrafish brain. Just how important this work by the two Freiburg-based researchers is for developmental neurobiology is reflected in the fact that the renowned journal Nature Methods deemed the procedure worthy of publication in its edition released at the end of June.

The nervous system is so complex that it was previously impossible to grasp it fully using classic scientific approaches. Scientists were usually only able to investigate one brain-influencing factor at a time, and could record no more than local changes triggered by it. However, once Wolfgang Driever and his team had succeeded in charting all the pathways formed in the zebrafish brain by a certain type of nerve cell – so-called dopaminergic nerve cells – only then was it possible for the group of computer scientists led by Olaf Ronneberger to construct a virtual, 3D model of the zebrafish brain, the "standard brain".

Their jointly developed "Virtual Brain Explorer for Zebrafish (ViBE-Z)" automatically allocates genetic data captured during experiments to predefined landmarks on a 3 D stack of brain image, the standard brain, taken under identical conditions. The detailed information provided by the brain image is used to compare the new data with the standard brain in the database. This is done automatically and with a level of accuracy that distinguishes between individual cells. In order for the comparison to take place, Olaf Ronneberger and his team are developing new computer processes that recognise anatomical structures in the zebrafish brain with a great degree of reliability and transfer them to the standard 3D brain. The scientists can then access the accompanying database to see which genes are active in certain areas of the brain and highlight the areas where different proteins influence brain activity under a diverse range of experimental conditions. Consequently, a large number of factors that simultaneously influence a particular area of the brain can now be viewed virtually and investigated in one integrated approach. "As a result, our understanding of the complicated 'brain network' is much better than it was in the past, and for the first time we have been able to quantitatively compare our data in a 3D space with that from labs in Tokyo and Washington, for example," explains Wolfgang Driever. The Freiburg-based researchers intend to make ViBE-Z accessible to all interested colleagues. Researchers from all over the world will be able to upload their images and genetic data onto the system via an online portal, and around half an hour later they will be able to download a virtual model calculated using this data in the standard brain from the server in Freiburg. Many of the developmental and neurobiological discoveries made in zebrafish can be transferred to humans, which make it a particularly favoured model organism among biologists and medics. There is, however, a further reason why Wolfgang Driever particularly enjoys working with Danio rerio, the Latin name for his preferred research subject. "The way in which processes can be visualised in the fish is simply beautiful. In other words: the knowledge you gain is also visually appealing." Driever's team generates images of the zebrafish brain using special microscopes. In addition to normal confocal laser scanning microscopes a new movable objective microscope (MOM) is also employed that allows images to be taken in living animals and penetrates layers 500 to 800 micrometres deep into the tissue. As the objective can be moved, the researchers can document processes over longer periods of time and they can even take images for electrophysiology studies in connection with those for behavioural experiments.

In 1996/97, Wolfgang Driever was the first person to perform genetic analyses of dopaminergic nerve cells in fish brains, a fact which reveals a lot about his character as a researcher: "Researching things that are little understood is what excites me most." Driever is particularly interested in dopaminergic neurons of the A11 system. These are difficult to study in humans as they are spread across different areas of the brain, and even experiments on mice have yielded very little information to date on these types of cells. On the other hand, these nerve cells have considerable influence on numerous processes in the brain. They form pathways in the most diverse cerebral areas, even into the spinal cord. As a result, although they make up less than 0.1% of all nerve cells, they modulate a vast number of circuits. The tiniest changes determined by these neurons, therefore, have major consequences and thanks to ViBE-Z it is



now possible to record these in their entirety and shape them into strong scientific statements. "This project fits wonderfully with the goals of the School of Life Sciences – LifeNet which aims to pursue the understanding of complex networks," he adds with evident delight.

Gaining a better understanding of the processes triggered by A11 neurons is also important since they play a critical role in the development of Restless Legs Syndrome and in controlling sensitivity to pain. The biologist does not harbour designs to heal the world, however. As the Internal Senior Fellow clearly stresses: "The work performed in my group is classic basic research". *(kb)*