Modelling the Brain

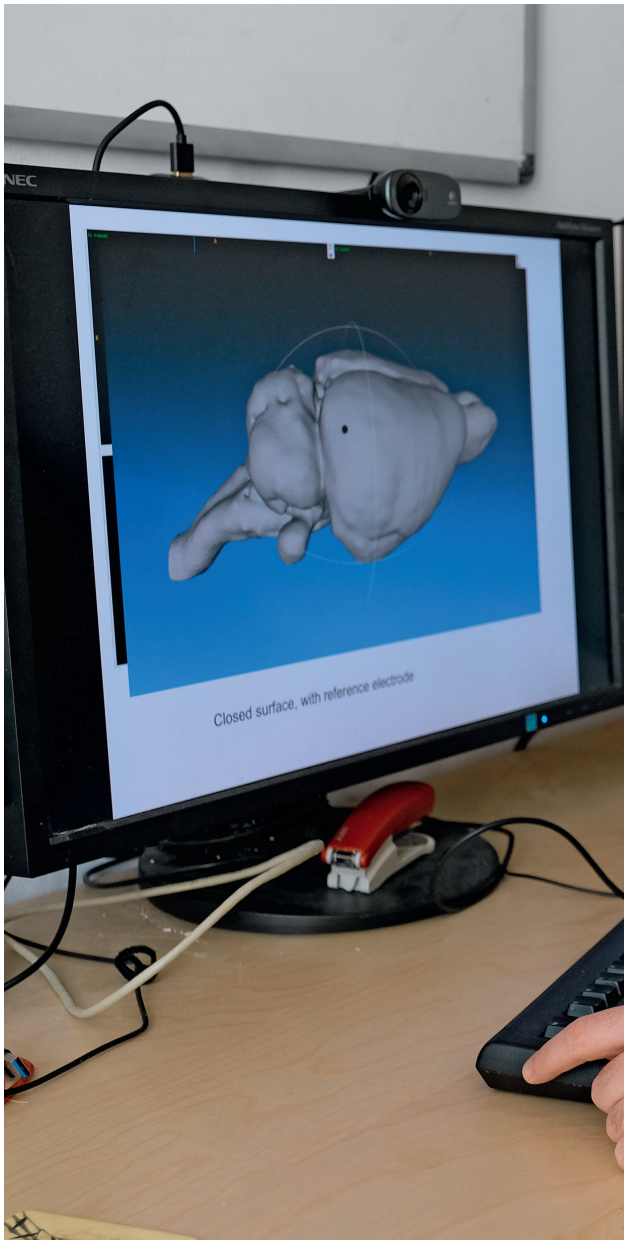
Prof. Daniel Wójcik from the Nencki Institute of Experimental Biology explains the principles of brain modelling.

ACADEMIA: **Where does the idea of using modelling in neurobiology come from?**
DANIEL WÓJCIK: I believe that modelling is the essence of contemporary science. The world is so complex that in order to make sense of it, we must focus on a selected fragment and ignore the rest. By choosing a fragment for analysis, we make certain arbitrary assumptions and thus establish a model, even if this is not intentional. Models can be quantitative or qualitative. For me, a model is generally a set of mathematical equations, but some of my colleagues see mice and rats as models of various processes in humans.

At which point does an isolated fragment of reality become a model?
Let's say there is a natural phenomenon we are trying to understand. We begin by describing it, starting from elements we see as important, and we search for their basic definitions. Next, we use this basic model to draw conclusions and compare them against observations and experimental data. If they are in agreement, it means the model works and we can use it to perform certain kinds of analysis that are difficult in real systems. There is an old saying that all models are wrong, but some are useful.

How do we determine whether a model is good?
It depends what we need the model for. Models help us elucidate certain phenomena, but they are by definition temporary because we are constantly expanding our knowledge. Let's look at models of our Solar System: Ptolemy's geocentric model was sufficient to explain many phenomena, while in the early days Copernicus' heliocentric model was not very useful in practice even though it reflects reality better.

We must also be prepared to reject our models. A model which we are unable to reject because



any measurement we could perform would always agree with it, is useless because it doesn't explain anything.

In my research, observations are recordings from electrodes placed in the brain. In order to interpret them, we have to take into account the cause/effect links between processes which occur in the brain and the signals we register. The detected signal originates from thousands, or millions of cells, so the model must take into account the physics of propagation of electromagnetic fields, the biochemistry of generation of membrane potential, etc. We frequently take mental shortcuts and ignore many of these processes, but we are aware that it is possible to verify or change our assumptions and simplifications.

Please tell us about how you model the workings of the brain.

There are two main strategies in brain modelling. One involves simplifying the phenomenon under investigation as much as possible, while the other is the opposite in that it attempts to recreate reality with as much detail as possible. The brain comprises around 100 billion cells which interpret incoming information and send binary "yes" or "no" signals. Of course, this is a major simplification. Each cell is a highly complex analogue computer processing data from tens of thousands of active input points at a rate of up to a hundred times per second. If we are interested in many cells, the problem becomes a major technical challenge. Additionally, the approach we use to create

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the most precise model of reality carries further conceptual problems. Will such a complex model really help us understand anything? If we were to construct a far simpler model, comprising, say, two elements but capturing the essence of the phenomenon under investigation, it could facilitate our understanding.

What's the smallest element of the models you work on?

We usually use compartment modelling, borrowing a term from engineering sciences. To explain this, let's start from cell morphology. Nerve cells – neurons – are characterized by dendritic trees with complex branching structures. We divide each tree into many fragments; they are approximately cylindrical, and a typical cell may comprise over ten thousand of them. A single cylinder is a structural unit of the model, known as a compartment. This is how we describe the overall structure; next we describe the function of individual fragments. The most important parameter in neuron function is the dynamics of the cell membrane, which in turn depends on ion channels. We describe them using Hodgkin-Huxley-like nonlinear differential equations. Each cell can comprise many different types of ion channels, and we describe each one using several variables.

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Each compartment – of which there may be thousands in a realistic cellular model – requires numerous differential equations describing the activity of a single fragment. The equations are interconnected because they model interconnected processes, such as the transmission of electrical potential or ions between neighboring compartments. The resulting description of cell membrane activity is realistic and acts as a fundamental level for our model.

The next stage is to describe communication between cells, for which we use models of cellular activity or models of synaptic activity. They take into account the sequence of biochemical changes which occur as synapses are activated and allow us to model, e.g. brain plasticity. If we want to create a realistic model of how the brain works, we have to also consider glial cells – the non-neuronal cells in the central nervous system. Glia have multiple functions: as well as maintaining homeostasis in the nervous system, recent research shows that they affect how information is processed, although the significance of this function is not clear.

Where do theorists obtain data for their models? Surely a biological structure is necessary.

Of course the data originates from experiments. In the past, every part of the description originated from a different sample – for example morphology, biophysical properties and channel expression would be studied in different specimen. Currently we are striving to obtain as much information as possible from a single cell. This requires state-of-the-art techniques and significant manpower; in such subtle applications, technical skills become an art form. Experimental data serves as a reference point. Technological progress means we are obtaining vast volumes of information, although it will always remain incomplete to some extent. Of course, in modelling, information is also incomplete, but in an entirely different way. Information modelling is largely complementary to experimental data. Such constant interaction between theory and experiment is the most fruitful approach to science.

Have you been constructing such complex models from the start?

I started at the Nencki Institute in 2003, where I met people who were interested in the processing of sensory information at the early stages of the sensory system in rats, which are often used as models of most sensory systems, including human. The study involved placing electrodes in the brains of rats to monitor the animals' responses to researchers stimulating their vibrissae (whiskers). The signal is picked up by the trigeminal nerve and transmitted to the thalamus and the cerebral cortex, then back to the thalamus. The processing of this information is complex, although we have a good understanding of the network involved with it. My colleagues were interested in whether the process is the same when the animal is habituated and stimulated.

First, rats were habituated to the stimulus; once the procedure became predictable and boring, they received a mild electrical shock to the ear. The aim was not to hurt the animals but to surprise them and indicate that something new had occurred. We wanted to find out whether the changed context affects how information is processed. It turned out we saw almost no difference in either the thalamus or the cerebral cortex. In order to understand this, we analyzed the recorded electrical potentials by reconstructing the activity of electrical sources, then breaking them down into independent components. The dominant components can be naturally tied with the activity of two specific populations of thalamus cells. The results we

obtained were rational and corresponded with our understanding of neurobiology. They were published, but because I am a theorist, I felt somewhat unsatisfied. We were told that the method we used reached beyond the scope of its applicability, because breaking down the results into independent components assumes that sources are independent, and this condition was not met. Also, it was still unclear what information was carried by the recorded signals – or, to put it another way, what the relationship is between the recorded stimulus and what happens in the animal's brain. Creating a good model reflecting actual brain activity from scratch requires years of efforts from a large team of scientists. We did not have the time or the resources, so we used a model of the system published by another team, which we adapted to our own needs. Researchers increasingly publish their models including the computer programs used to create them alongside their results. This allows others to use and adapt them, which facilitates scientific development. In this instance, we used a model of the thalamo-cortical loop, which is the simplest model of the early stages of sensory information processing, developed by Roger Traub from IBM. We adapted the model to fit our problem to simulate the responses of a virtual sensory system to stimulation of virtual whiskers.

What happens to this model? How is it studied?

In our model, we simulated electrical impulses in thalamic cells, which corresponded to stimulating vibrissae, and observed what happens to the information in the thalamo-cortical loop. Signals arriving to the cortex were similar to those registered by the electrodes placed in the brain of a real rat. The following step was to modulate the input signal to see how the model performs. In quantitative terms, results obtained from the model are never exactly the same as those from a real brain. However, we have reasons to believe that the relationship between the modelled signal and the activity in our virtual system is similar to what happens in reality. Our models do not allow us to draw conclusions on the functioning of real rat brains, but I believe their complexity is similar to actual signals. Since we control the relationships between the activity of the given signal and simulated measurements, we can use the data to validate data-analysis methods which we can later apply to data from real experiments. Such validation gives us strong foundations to interpret the results of experimental data analysis, which in turn means we can draw conclusions which reflect reality.

To finish, please tell us about large modelling projects such as the Human Brain Project.

The traditional approach to neurobiological research is to select our favorite cell, structure, or paradigm and then to study it. If it is the first cell of its kind, or the first in a given structure, the PhD student who found it publishes the results in *Nature*. A subsequent cell from the structure can perhaps make it to the *Journal of Neuroscience* if the reviewers find something of interest, whereas the third cell is unlikely to elicit any interest. If we want to discuss the properties of populations of cells, we can't simply study a few individual cells – we must investigate hundreds or thousands. Several years ago researchers began to realize that they need to break away from the traditional paradigm of brain research since existing methods were not suited to certain tasks. If we are interested in the properties of large populations of cells, we need to work on a major, international scale. These were the origins of the European Human Brain Project, the Brain Initiative in the US and similar projects in Japan and China. There are also several private initiatives: for example, the late Paul Allen, one of the co-founders of Microsoft, financed the Allen Institute of Brain Science whose mission is to systematically map the properties of the brain. Some of the institution's first achievements were the development of brain atlases and morphological and structural descriptions; their latest project is MindScope whose aim is to provide a quantitative taxonomy of cell types in all structures of the brain. Perhaps the greatest aspect of the project is the principle that all data, fully cleaned and described, is available online – frequently before it is even published – which means that all researchers around the globe have full access to it.

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The Blue Brain Project and the Human Brain Project originally only released the results of simulations, but this has also changed. The only question remaining for researchers is *when* to make their data available. After all, it is possible to continue publishing results based on collected and processed data, and only release raw data when it is fully exploited. Luckily the situation is improving: state-of-the art software is being developed to read and process data, and to allow different centers and platforms around the globe to connect with one another.

INTERVIEW BY **DR. AGNIESZKA KLOCH**