Will technology deliver for 'big neuroscience'?

European and US initiatives aiming to improve our understanding of the brain will require important leaps in technological development.

To many, 'brain' is the new 'genome'. Having completed the big sequencing challenge of the nineties and early aughts, some political institutions seem ready to undertake another big and collective scientific endeavor—this time, to improve our understanding of how human brains work.

In January, the European Commission announced that it would give €1 billion to a project aiming to simulate the human brain, the Human Brain Project. This project seeks to integrate everything we know about the brain into massive databases and detailed computer models. Following this announcement, the US National Institutes of Health unveiled their desire to undertake a project of no less magnitude that seeks to monitor the activity of whole brains at the cellular level: the Brain Activity Map.

Both of these projects require, first and foremost, leaps in technological development. The Human Brain Project will need substantial advancements in algorithms and computing technology. There is also the question of whether sufficient quantities and quality of data exist to create accurate models. The Brain Activity Map will require new functional imaging or recording technologies, better probes for measuring brain activity at the cellular level and software to make sense of the data. Its proponents must also manage expectations with regard to which organisms' brains it can tackle.

The challenges with the brain are that it functions at the level of cells and synapses and that communication happens on the millisecond timescale. Technologies do exist to record the activity of hundreds of cells located in a relatively small region of the brain with high spatial and temporal resolution in model organisms, using either imaging approaches or electrodes. But interesting brain functions emerge from the interaction of thousands or perhaps millions of neurons distributed across the entire brain. Imaging technologies, such as functional magnetic resonance imaging (fMRI), can infer neuronal activity across the entire brain in a noninvasive manner, but their resolution is currently much too coarse to unveil what is going on at the cellular level. Thus, there is clearly a gap in what current technology can do for whole-brain studies at the level that matters most.

An article published online in this journal has taken landmark steps toward closing this technology gap—at least for some model organisms. In this work, Philipp Keller and Misha Ahrens apply light-sheet microscopy to image the activity of 80% of the neurons in the brain of the fish larva at almost a whole brain per second.

The significance of this work is that one can now functionally observe almost all cells of a vertebrate brain with single-cell resolution and on the timescale of neuronal activity patterns and behavior. This technology opens new possibilities for observing entire circuits in action, which, in combination with optogenetics for studying their causal role in behavior and with anatomical tracing methods, will permit a new level of understanding of brain function.

Undertaking these types of experiments may be possible within the next 5–10 years in organisms whose brains are largely transparent to visible light, such as the zebrafish larva or the worm *Caenorhabditis elegans*. But the translation of this technology into mice—not to mention humans—is an entirely different ball game.

The mouse brain has at least ten times more cells than the larval brain of a zebrafish. It is also protected by a thick, light-impenetrable skull. Imaging the mouse brain from the surface after surgical removal of the bone poses challenges because light penetration is limited. Using infrared light and correcting for tissue-induced aberrations will enable deeper probing into the mammalian brain but requires improvements to existing microscopy methods. In parallel, probes that respond to infrared light, both for activity monitoring and intervention, will need to be developed. This type of imaging approach, from the surface down, will let us see only a small fraction of the whole brain, however. To image whole mammalian brains in action at the cellular level in a noninvasive manner, entirely new methods must be invented. Alternatively, the resolution of approaches such as fMRI will need to be significantly improved.

When the Human Genome Project started, there was a methodology, albeit a slow one, in place that could be used to reach the project's goal. The collective push toward this challenge generated great technological improvements; and even today, years after the main goal was achieved, technological development in the field of genomics is still booming.

The neuroscience projects, however, are in graver need of technological advances to generate the desired data. These are exciting times for neuroscience research. More than ever, inclusive discussions among physicists, engineers and especially neuroscientists across the globe will be critical if we are to successfully reach the ambitious goals on the agenda.