Simulating the human brain

Scientists have started various major projects to simulate and understand the brain, but many neuroscientists remain sceptical about their scope and aims

Philip Hunter

Over the past few years, neurological research has spawned various large-scale research projects that aim to map and understand the function of the brain. Major research regions, including the USA, Europe, China and Japan, have either already begun such large-scale projects, or plan to do so soon. Although their methodologies and approaches differ, these projects aim both to understand how the human brain works and to develop more effective treatments for neurological conditions and cognitive disorders, from anxiety to Alzheimer's disease. The projects are inspired by the genuine hope that we are on the verge of a revolution in neurological research, but they have also courted controversy. This is especially the case for the European Human Brain Project (HBP) and, to a lesser extent, the US Brain Initiative (BI), partly because they are so big—in terms of money invested and people involved—and have inevitably grand ambitions that their critics argue might not be realized during their course.

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“It is a worry we may be over ambitious”, conceded Rafael Yuste, Director of the Neuro Technology Centre at Columbia University, New York, USA, and an advisor to the BI council. The BI emerged from the earlier Brain Activity Map (BAM) project, after endorsement by President Obama in

April 2013, and is now easily the best funded brain mapping project. The US government has pledged US \$100 million for the first year, US \$300 million for the second and US \$500 million for the third, then to remain at that level for a decade. The funding is subject to annual review, Yuste noted, but the prospects of sustained funding are good because the project enjoys bipartisan support from both Democrats and Republicans. The main focus of the BI lies in gathering more informative data from real-time imaging, while developing and testing clinical therapies for various disorders, of both the central and peripheral nervous system.

The HBP will also receive significant funding—with an estimated budget of €1.2 billion over 10 years (https://www.humanbrainproject.eu/en_GB/-/the-human-brain-project-begins)—and is arguably even more ambitious in scope: the goal, as originally stated, is to build a working model of the human brain on a supercomputer within 10 years. However, this aim of simulating the human brain has been criticized by many neuroscientists as impossible to achieve—or even to define—given the present state of knowledge. As a result, more than 150 leading neuroscientists (<http://www.neurofuture.eu/>) signed an open letter in July last year, urging the EU to divert funding away from the HBP towards smaller investigator-driven projects. The signatories also complained about the omission of cognitive neuroscience from the core part of the project.

One signatory to that letter, Jim Bednar, from the Institute for Adaptive and Neural Computation School of Informatics at the University of Edinburgh

in the UK, hopes that the HBP will succeed, but fears it cannot, unless it is scaled down into smaller projects with more realistic goals. “In theory, yes, the ideal brain model would integrate all the various levels, finally making sense of the mountain of neuroscience data that grows ever-larger without yet adding up to increased understanding”, Bednar said of the HBP's goal to analyse data at all levels of the brain, from molecules to neurons to networks to functions and disorders, and then integrate these into a single model. “In practice, the question is whether the HBP, or any single, massive, unified program with a fixed time scale, could ever achieve that, plus whether it is the right mechanism to do so, and whether it is the right time to do it. As for software projects, much less ambitious goals are much more likely to succeed, integrating across one, two, or three levels at first, with small networks of people who don't spend all their time exchanging reports and documenting milestones. Just trying to do everything in one big bang, without the right data to constrain each of the levels, is quite unlikely to achieve anything but spending piles of money”.

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Bednar also shares a view common among neuroscientists, which is that it is futile to attempt to build a complete brain

model now, when so little is known about the fundamental workings of the brain, even at the circuit level, never mind the emergent higher-level cognitive functions. The key point here, according to Stephen Van Hooser, Assistant Professor of Biology Development at Brandeis University in the USA, is that a neural circuit of any animal is much more than just a wiring diagram. “First, even if one knew all of the connections among neurons in a network, one must understand the operating principles of the elements that are connected and how the elements are modified by neuromodulators or other factors”, he said. “We have known the complete wiring diagram of the nematode *C. elegans* since the mid-1980s, but we still don’t understand the operating principles of its circuitry”. Many neural circuits also change over time, “[s]o one must understand the rules that govern how these circuits are modified by experience and their own activity”, he added. As such, there is still much to do to understand even the basic operating principles of a neural circuit. “This is truly a compelling problem that requires

creative problem solving and an interaction of modelling and experiments that defies easy categorization”, he said.

However, not all neuroscientists think that big projects such as the HBP should focus on fundamental questions before attempting to develop integrated brain models; some see scope for moving in parallel, providing expectations are kept in check. The EU has just completed its first yearly review of the HBP (<http://ec.europa.eu/programmes/horizon2020/en/news/1st-technical-review-human-brain-project-hbp-main-conclusions-recommendations>), which has taken account of the criticisms, but is nonetheless positive about the overall direction of the project. The report does recommend changes, however, and the original three-person executive committee that was running the project has been disbanded. Instead, executive decisions are now made by a board of directors, with the aim of reflecting broader opinion within the neuroscience research community. Moreover, cognitive neuroscience has been brought

back into the core project. The EU has also indicated that the project might not be wound up at the end of its 10-year term, around 2023, but that it could live on as a permanent pillar for brain research, funded by an international consortium of interested states comparable to CERN or EMBL.

“Taking account of the feedback has helped enormously with making people feel comfortable with the project”, said Richard Frackowiak, Head of Clinical Neurosciences at the Université de Lausanne in Switzerland (UNIL) and now Co-Director of the HBP. He thinks it is important to reassure neuroscientists that money will not be taken away from basic research, and to point out that the funding for HBP comes from computer science budgets. He also supports the project’s scope and said that data mining and computer simulation are now advanced enough to start generating a conceptual framework of the whole brain. “We need a very high level of informatics expertise to achieve that and also the maths that goes with that, especially in machine learning and sophisticated statistical techniques, to deal

with the complex models that the human mind itself is not capable of imagining”.

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The first 3 years of the HBP are devoted to building the informatics infrastructure, but with an emphasis on data analysis rather than collection, which has attracted criticism for being premature.

One challenge though that is being addressed by both the HBP and the BI is that a sounder basis for therapeutic development and drug discovery needs to be developed across the whole spectrum of neurological conditions. “On the one hand we are concerned with the societal problems of old age, but on the other the persistent issues of psychiatric disorders in the young. So far many attempts at therapies have been ill conceived and there have been no major advances since the 1950s”, Frackowiak said. He suggested that the HBP would be ready to make progress on the therapeutic front towards the second half of its 10-year term when the informatics platforms were in place. “Then we will be seriously looking at how we classify diseases more effectively in the post informatics era”.

Frackowiak reported that the HBP will aim to identify the underlying genetic causes of neurological conditions, as well as the complex epigenetic and other mechanisms linking those causes to symptoms. “We know that a single mutation can present as multiple phenomena”, he explained. “But at the same time, a single syndrome can be due to any of up to 25 different unrelated mutations. So we need to get a biologic foundation to diagnostic categories and then start using biologic information to think about drug targets more rationally, using the added precision of diagnosis to think about how we run clinical trials and how we create the various groupings”. As one example of how this might work, he cited Parkinson’s disease, in which symptoms only develop when around 70% of a particular set of neurons have been lost.

“There’s great opportunities there, because if you could get at things accurately pre-clinically, then you might be able to do a lot of good”.

Nevertheless, therapies are not the primary goal of the HBP, according to Katrin Amunts, a neuroscientist at the Jülich Research Centre in Germany and one of the HBP’s directors. She does expect that findings from the HBP will eventually have pharmaceutical applications, however, as the project will identify new molecular targets aligned with specific conditions. “I’m working on the distribution and concentration of neural transmitter receptors and these are the key elements on which all pharmaceutical agents bind”, Amunts explained by way of example. “Knowing how these receptors are distributed and balanced between different regulatory, inhibitory or modulatory receptors is a very important prerequisite for clinical work and has direct consequences for drug development”.

In contrast, the BI project in the USA has more immediate clinical objectives and is already fanning out in a variety of directions. One of these, the Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program (<http://www.darpa.mil/NewsEvents/Releases/2014/05/27a.aspx>), is being funded by DARPA, the research arm of the US military, whose involvement has been another source of controversy. The main aim is to train patients to regain lost movement of limbs by retraining their brains with the help of feedback from implants. “DARPA has taken a lead here to try and help war veterans”, Yuste said. “There is a suite of different methods, using implants both to read brain activities and stimulate the brain to help restore movement of limbs”. According to Yuste, this approach builds on pioneering work done by John Donoghue and colleagues at Brown University in Providence, Rhode Island, USA, on brain/machine interfaces in humans [1]. “DARPA wants to move to the next generation, with more selectivity and power and greater sophistication in the brain/machine interface”.

Yuste feels that recent developments in neuroscience have left him in a strange dichotomy between being pessimistic over the abject failure of neuroscience to come up with significant therapeutic advances and optimism over future prospects. He thinks that data from imaging

studies are finally creating the potential for major advances, providing it is integrated across all relevant scales. “We realized that we have been looking at the brain at the wrong scale, one layer at a time. I’m convinced that we need to be looking at the whole building rather than its bricks and atoms”, he said.

“... the application of graph theory to neural imaging has already begun to elucidate mechanisms underlying cognitive disorders”

This sounds remarkably like what the European HBP is aiming for, but the emphasis of the BI is much more on collecting real-time data from live brain images. “In the last 18 months, three different groups have obtained images of activities of every single neuron of a small animal. One is the hydra or jelly fish, one the worm *C. elegans* and one more complex being a vertebrate, the zebra fish”. All were chosen partly because they are transparent, making it possible to effectively observe neural activities while the animal is alive. “The resulting data is a turning point”, Yuste explained. “It will lead to progress in making brain activity maps of increasingly complex species”. One possible therapeutic target could be epilepsy, where the only current effective treatment for severely affected patients is to remove a portion of the brain, with significant cognitive side effects. If the brain could be imaged during a seizure, it might be possible to intervene and inactivate the relevant neurons without causing significant side effects. Yuste highlighted recent developments in light microscopy, such as light-sheet microscopy, as crucial for being able to take live movies of brains in action [2]. In humans, however, the skull prevents the application of this technique; solving that conundrum is one of the aims of the BI project.

Data alone, no matter how extensive and sophisticated, will not be sufficient to achieve the goals of the various brain projects. The projects all aim to make sense of the data at all levels, and particularly to establish links between patterns of neural activity and cognitive

functions. This is where informatics and mathematics come in to play, and some progress has already been made. One successful mathematical technique in use is graph theory, which has been used to analyse the correlation between neural network connectivity and psychiatric disorders. Graph theory is the study of graphs involving nodes or points and the lines or edges joining them. It is applicable to biological neural networks, where the nodes are neurons and the interconnecting lines are axons and synapses.

According to Stephan Eliez, Director of Child Psychiatry and Special Education at the University of Geneva School of Medicine in Switzerland, the application of graph theory to neural imaging has already begun to elucidate mechanisms underlying cognitive disorders. He gave the example of a study in which graph theory was used to assess the link between brain structure and schizophrenia, the main symptom of which is hallucination [3]. The authors of the study used magnetic resonance imaging (MRI) scans of 46 patients, along with 48 controls, to create a whole brain network for each individual, and applied graph theory to quantify both the local and global

connectivity of each brain. The study found that the schizophrenic patients had an average of 6% less global brain connectivity and that 58% of their local neuron hubs also suffered from impaired connectivity, providing strong evidence of a link between neural network structure and schizophrenia. In fact, neuron hubs have recently been identified as key features of brains in humans and other mammals, coordinating activity across the whole distributed neural network [4]. The authors argue that their results provide preliminary evidence that the brain network hub organization in individuals with a genetic risk for schizophrenia is altered in a targeted way.

This is just one example of how collaboration between neurobiologists and mathematicians—a premise originally spurned by the HBP—can yield interesting and potentially applicable results, providing a glimpse of what might emerge from the brain mapping projects over the next decade. Only time will tell, however, whether the HBP and the BI will live up to their promise to generate new knowledge about how the human brain works, and whether this knowledge will lead to valuable clinical insights or applications. For now, the

restructuring and refocussing of the HBP has appeased some of its critics and given the project a new way forward. Even so, many neuroscientists remain sceptical that any single large-scale project will be able to deliver effectively on such a multifaceted and complex problem as the human brain.

References

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