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BRAIN IN A BOX

Henry Markram wants €1 billion to model the entire human brain. Sceptics don't think he should get it.

BY M. MITCHELL WALDROP

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It wasn't quite the lynching that Henry Markram had expected. But the barrage of sceptical comments from his fellow neuroscientists — "It's crap," said one — definitely made the day feel like a tribunal.

Officially, the Swiss Academy of Sciences meeting in Bern on 20 January was an overview of large-scale computer modelling in neuroscience. Unofficially, it was neuroscientists' first real chance to get answers about Markram's controversial proposal for the Human Brain Project (HBP) — an effort to build a supercomputer simulation that integrates everything known about the human brain, from the structures of ion channels in neural cell membranes up to mechanisms behind conscious decision-making.

Markram, a South-African-born brain electrophysiologist who joined the Swiss Federal Institute of Technology in Lausanne (EPFL) a decade ago, may soon see his ambition fulfilled. The project is one of six finalists vying to win €1 billion (US$1.3 billion) as one of the European Union's two new decade-long Flagship initiatives.

"Brain researchers are generating 60,000 papers per year," said Markram as he explained the concept in Bern. "They're all beautiful, fantastic studies — but all focused on their one little corner: this molecule, this brain region, this function, this map." The HBP would integrate these discoveries, he said, and create models to explore how neural circuits are organized, and how they give rise to behaviour and cognition — among the deepest mysteries in neuroscience. Ultimately, said Markram, the HBP would even help researchers to grapple with disorders such as Alzheimer's disease. "If we don't have an integrated view, we won't understand these diseases," he declared.

As the response at the meeting made clear, however, there is deep unease about Markram's vision. Many neuroscientists think it is ill-conceived, not least because Markram's idiosyncratic approach to brain simulation strikes them as grotesquely cumbersome and over-detailed. They see the HBP as overhyped, thanks to breathless media reports about what it will accomplish. And they're not at all sure that they can trust Markram to run a project that is truly open to other ideas.

"We need variance in neuroscience," declared Rodney Douglas, co-director of the Institute for Neuroinformatics (INI), a joint initiative of the University of Zurich and the Swiss Federal Institute of Technology in Zurich (ETH Zurich). Given how little is known about the brain, he said, "we need as many different people expressing as many different ideas as possible" — a diversity that would be threatened if so much scarce neuroscience research money were to be diverted into a single endeavour.

Markram was undeterred. Right now, he argued, neuroscientists have no plan for achieving a comprehensive understanding of the brain. "So this is the plan," he said. "Build unifying models."

> "IT WILL BE LOTS OF EINSTEINS COMING TOGETHER TO BUILD A BRAIN."

MARKRAM'S BIG IDEA

Markram has been on a quest for unity since at least 1980, when he began undergraduate studies at the University of Cape Town in South Africa. He abandoned his first field of study, psychiatry, when he decided that it was mainly about putting people into diagnostic pigeonholes and medicating them accordingly. "This was never going to tell us how the brain worked," he recalled in Bern.

His search for a new direction led Markram to the laboratory of Douglas, then a young neuroscientist at Cape Town. Markram was enthralled. "I said, 'That's it! For the rest of my life, I'm going to dig into the brain and understand how it works, down to the smallest detail we can possibly find.'"

That enthusiasm carried Markram to a PhD at the Weizmann Institute of Science in Rehovot, Israel; to postdoctoral stints at the US National Institutes of Health in Bethesda, Maryland, and at the Max Planck Institute for Medical Research in Heidelberg, Germany; and, in 1995, to a faculty position at Weizmann. He earned a formidable reputation as an experimenter, notably demonstrating spike-timing-dependent plasticity — in which the strength of neural connections changes according to when impulses arrive and leave (H. Markram *et al. Science* **275,** 213–215; 1997).

By the mid-1990s, individual discoveries were leaving him dissatisfied. "I realized I could be doing this for the next 25, 30 years of my career, and it was still not going to help me understand how the brain works," he said.

To do better, he reasoned, neuroscientists would have to pool their discoveries systematically. Every experiment at least tacitly involves a model, whether it is the molecular structure of an ion channel or the dynamics of a cortical circuit. With computers, Markram realized, you could encode all of those models explicitly and get them to work together. That would help researchers to find the gaps and contradictions in their knowledge and identify the experiments needed to resolve them.

Markram's insight wasn't original: scientists have been devising mathematical models of neural activity since the early twentieth century, and using computers for the task since the 1950s (see page 462). But his ambition was vast. Instead of modelling each neuron as, say, a point-like node in a larger neural network, he proposed to model them in all their multi-branching detail — down to their myriad ion channels (see 'Building a brain'). And instead of modelling just the neural circuits involved in, say, the sense of smell, he wanted to model everything, "from the genetic level, the molecular level, the neurons and synapses, how microcircuits are formed, macrocircuits, mesocircuits, brain areas — until we get to understand how to link these levels, all the way up to behaviour and cognition".

The computer power required to run such a grand unified theory of the brain would be roughly an exaflop, or 10^{18} operations per second — hopeless in the 1990s. But Markram was undaunted: available computer power doubles roughly every 18 months, which meant that exascale computers could be available by the 2020s (see 'Far to go'). And in the meantime, he argued, neuroscientists ought to be getting ready for them.

Markram's ambitions fit perfectly with those of Patrick Aebischer, a neuroscientist who became president of the EPFL in 2000 and wanted to make the university a powerhouse in both computation and biomedical research. Markram was one of his first recruits, in 2002. "Henry gave us an excuse to buy a Blue Gene," says Aebischer, referring to a then-new IBM supercomputer optimized for large-scale simulations. One was installed at the EPFL in 2005, allowing Markram to launch the Blue Brain Project: his first experiment in integrative neuroscience and, in retrospect, a prototype for the HBP.

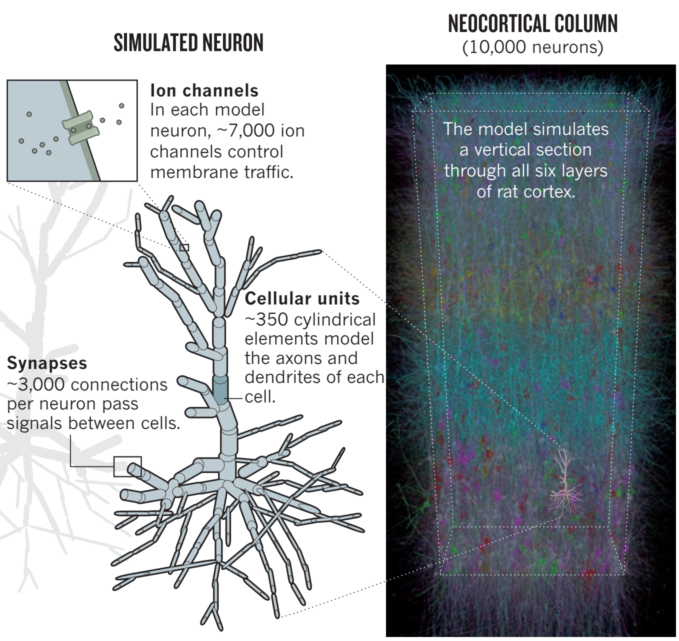
Part of the project has been a demonstration of what a unifying model might mean, says Markram, who started with a data set on the rat cortex that he and his students had been accumulating since the 1990s. It included results from some 20,000 experiments in many labs, he says — "data on about every cell type that we had come across, the morphology, the reconstruction in three dimensions, the electrical properties, the synaptic communication, where the synapses are located, the way the synapses behave, even genetic data about what genes are expressed".

By the end of 2005, his team had integrated all the relevant portions of this data set into a single-neuron model. By 2008, the researchers had linked about 10,000 such models into a simulation of a tube-shaped piece of cortex known as a cortical column. Now, using a more advanced version of Blue Gene, they have simulated 100 interconnected columns.

The effort has yielded some discoveries, says Markram, such as the as-yet unpublished statistical distribution of synapses in a column. But its real achievement has been to prove that unifying models can, as promised, serve as repositories for data on cortical structure and function. Indeed, most of the team's efforts have gone into creating "the huge ecosystem of infrastructure and software" required to make Blue Brain useful to every neuroscientist, says Markram. This includes automatic tools for turning data into simulations, and informatics tools such as http://channelpedia.net — a user-editable website that automatically collates structural data

BUILDING A BRAIN

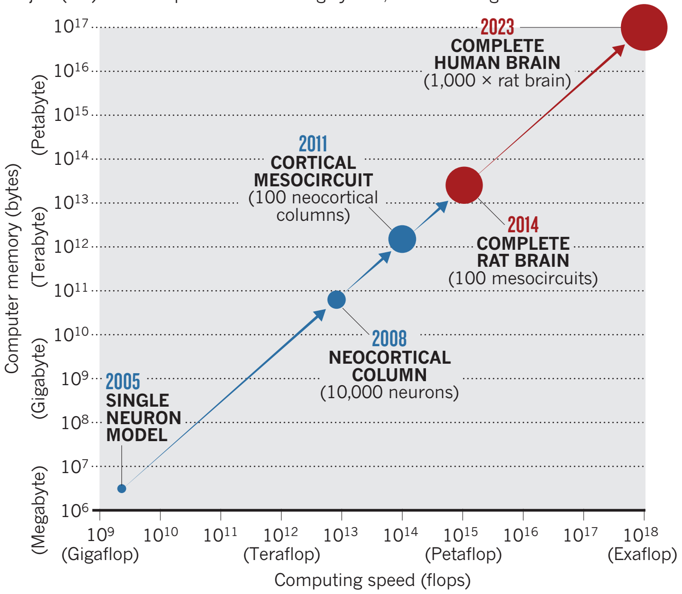
The Blue Brain simulation — a prototype for the Human Brain Project — constructs simulated sections of cortex from the bottom up, starting from detailed models of individual neurons.



SOURCE: BBP/EPFL

FAR TO GO

The Blue Brain Project has steadily increased the scale of its cortical simulations through the use of cutting-edge supercomputers and ever-increasing memory resources. But the full-scale simulation called for in the proposed Human Brain Project (red) would require resources roughly 100,000 times larger still.



SOURCE: BBP/EPFL

on ion channels from publications in the PubMed database, and currently incorporates some 180,000 abstracts.

The ultimate goal was always to integrate data across the entire brain, says Markram. The opportunity to approach that scale finally arose in December 2009, when the European Union announced that it was prepared to pour some €1 billion into each of two high-risk, but potentially transformational, Flagship projects. Markram, who had been part of the 27-member advisory group that endorsed the initiative, lost no time in organizing his own entry. And in May 2011, the HBP was named as one of six candidates that would receive seed money and prepare a full-scale proposal, due in May 2012.

If the HBP is selected, one of the key goals will be to make it highly collaborative and Internet-accessible, open to researchers from around the world, says Markram, adding that the project consortium already comprises some 150 principal investigators and 70 institutions in 22 countries. "It will be lots of Einsteins coming together to build a brain," he says, each bringing his or her own ideas and expertise.

BOTTOM TO TOP

The description of the HBP as an open user facility sparked interest and enthusiasm at the Bern meeting. But much more vocal were Markram's critics, many of whom focused on the perceived inadequacies of the Blue Brain model — and of Markram's approach to data integration.

At the heart of that approach is Markram's conviction that a good unifying model has to assimilate data from the bottom up. In his view, modellers should start at the most basic level — he focuses on ion channels because they determine when a neuron fires — and get everything working at one level before proceeding to the next. This requires a lot of educated guesses, but Markram argues that the admittedly huge gaps in knowledge about the brain can be filled with data as experiments are published — the Blue Brain model is updated once a week. The alternative approach, approximating and abstracting away the biological detail, leaves no way to be sure that the model's behaviour has anything to do with how the brain works, said Markram.

This is where other computational neuroscientists gnash their teeth. Most of them are already using simple models of individual neurons to explore high-level functions such as pattern recognition. Markram's bottom-up approach risks missing the wood for the trees, many of them argued in Bern: the model could be so detailed that it is no easier to understand than the real brain. And that is if Markram can build it at all. Judging by what Blue Brain has accomplished in the past six years, critics said, that seems unlikely. The tiny swathe of simulated rat cortex has no inputs from sensory organs or outputs to other parts of the brain, and produces almost no interesting behaviour, pointed out Kevan Martin, co-director of the INI, in an e-mail. It is "certainly not the case" that Markram has simulated the column as it works in a whole animal, he said.

Markram's response to such criticisms in Bern was that more capabilities are always being added to the Blue Brain simulation. But Martin remained unimpressed. "I cannot imagine how this level of detail, which is still very incomplete even after Henry's considerable labours, is ever going to be obtained from more than a few regions of the rodent brain in the next decade, let alone brains of *Drosophila*, zebrafish, songbird, mouse or monkey," his e-mail continued.

"Of course," Martin added, "all this would be but a storm in the professors' teacups" if the HBP hadn't come along and raised the stakes enormously. It is all too easy to imagine other areas of neuroscience research being starved for resources by the HBP — especially in Switzerland, which as host country will have to provide a substantial, but still-undetermined, fraction of the funding. Douglas asks: should Europe be spending €1 billion to support the passionate quest of one man? He concedes that visionaries are sometimes necessary to drive progress. "But what if they're passionately wrong?"

Also fuelling anxiety — and irritation — is the widespread sense that Markram has been making his case through the news media, not through publishing, conferences and the other conventional channels of science. Reporters see much to like: Markram is tall, striking and explains his ideas with the clarity, quotability and urgency of a South African version of the late Carl Sagan. He has "a hypnotic effect", says Richard Hahnloser, a computational neuroscientist at the INI. But critics say that this results in too many news accounts that leave the impression that the HBP will, say, eliminate the need for experimental animals.

"The whole neuroscience community will be in trouble ten years from now" when the implied predictions don't come true, says another INI researcher, who worries that the politicians will be right there saying, "But you promised!"

MARCH OF PROGRESS

In Bern, Markram bristled at accusations that he has deliberately cultivated hype. "I have never said that the HBP would replace animal experiments," he shot back at one questioner. "I said that simulation helps you choose the experiments that will best add value."

Markram was also at pains to insist that the HBP will be open to other modelling approaches. "This concern is unfounded because they simply have not bothered to find out what is being proposed," he told *Nature* after the meeting. The final facility "will allow anyone to build models at a range of levels of biological detail with as much data as possible from anywhere".

Markram seems to be building support. Last year, the board that oversees both the ETH and the EPFL enthusiastically endorsed the Blue Brain Project after a rigorous review by a four-member panel that included two outspoken sceptics of Markram's approach. The board asked the Swiss parliament to commit 75 million Swiss francs (US$81 million) to the project for 2013–16 — more than ten times Blue Brain's current budget. Parliament's decision is expected next month.

Markram is optimistic that the European Union will come to much the same conclusion about the HBP. However, if the project isn't endorsed, says Markram, "we'll just continue with Blue Brain" — although it may take a lot longer to reach a full brain simulation.

Markram clearly feels that history is on his side. "Simulation-based research is an inevitability," he declared in Bern. "If I get stopped from doing this, it's going to happen. It has happened already in many areas of science. And it is going to happen in life science." ■

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