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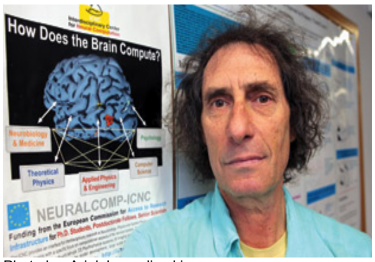

Photo by: Ariel Jerozolimski

The Israeli mind behind the Blue Brain Project

By JUDY SIEGEL-ITZKOVICH
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HUJI neuroscientist Prof. Idan Segev says the real breakthrough in brain science will be at least as momentous as the Industrial Revolution.

To understand exactly how the human brain – the most complex machine in the universe – actually works, takes more than ordinary brain power. A team that should eventually comprise thousands of staffers around the world using a supercomputer combining the computational power of 10,000 PCs is expected to reach its goal in about two more decades. And Israelis – led by the Hebrew University of Jerusalem's Prof. Idan Segev – are playing a key role in this effort, which is aimed not only at understanding the brain – with its hundreds of billions of neurons – but also at repairing diseased cells and tissues.

Perhaps in only a few years, scientists devoting themselves to the Blue Brain Project based in Lausanne, Switzerland are expected to learn enough from their work on mouse brains to make a big difference in both basic neurological science and clinical treatment at the bedside.

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Segev, formerly head of HU's neurobiology department in the Silberman Institute of Life Sciences and co-founder and previously director of the Interdisciplinary Center for Neural Computation, has spent most of his life and career on the university's Givat Ram campus, . There he received his bachelor's degree in mathematics and biology, his master's of science degree in neurobiology and his doctorate in experimental and theoretical neurobiology (the last two with highest honors).

Later, he spent a few years doing research at the US National Institutes of Health (NIH) and a few months at the Massachusetts Institute of Technology, but understanding the brain while working at the Jerusalem campus has been his vocation and obsession.

He decided to forgo his management work two years ago to concentrate on being a "plain scientist and professor."

Since 2001, he has been one of the leaders of the Blue Brain Project, the only participant to have a direct line to the Swiss IBM supercomputer, which costs $20 million and whose cooling alone with Geneva lake water has an annual price tag of $1 million. The supercomputer, he says, takes up about twice the area of his own office. Segev not only goes to Switzerland a few times a year; he and his six advanced neuroscience students also participate in weekly videoconferences for consultation and collaboration. The Jerusalem center for neural computation is the largest and most important of its kind in the world.

Segev's funding comes from Israeli and international grants, including the NIH. The Edmond J. Safra Philanthropic Foundation headed by his widow, Lily Safra – who donated to HU for the establishment of the $130 million Edmond and Lily Safra Center for Brain Sciences – has given $50 million.

"We promised we would be among the world's five top brain research centers in the world, and they are actively involved in supervising our work," Segev says. New nodes of the Blue Brain have opened in Spain and in France, with another one due to be launched in the Far East. "We have a fantasy that the whole world will eventually break political borders and focus on circuits in the brain," Segev says.

Neural computation is a new research field that focuses on how the nervous system's processes sensory information (vision, hearing and touch) and creating appropriate behavioral output. "But how does the brain go about it computation?" he asks. "How do the physical components of the nervous system – the ion channels in the neural membrane, the synapses and neural transmitters that connect the neurons, the electrical signals (the spikes) that neurons carry and the uniquely structured nerve cells and the large networks created by them – perform the task of computing? This mystery is, perhaps, the greatest intellectual challenge of the 21st century. The field of neural computation has made this challenge its goal.

"The brain is living proof that physical, chemical, and electrical components can display highly developed levels of intelligence," Segev states. "It processes and computes information!" But how do the billions of cells that make up the human brain control the functioning of the body, movement, memory, emotions, and the performance of creative tasks?

Neuroscience in the 20th century "was noted for the development of sophisticated techniques that gave us an inside view of the nervous system at different levels. The invention of the electron microscope in the 1950s allowed scientists to identify types of synapses and pinpoint their location on the dendrite," Segev adds.

But now, he says, "the time has come to synthesize – to go beyond the enormous achievements of the 20th century in exploring neural mechanisms at the anatomical, physiological and molecular levels – and develop a theory or working model that connects the mechanistic level that we became intimately acquainted with and the behavioral level. We need to synthesize the biological details of the brain into its emergence psychological capabilities – this requires a new mathematical theory for this amazing machine."

Progress in these multidisciplinary fields "will allow us to exchange parts of a living brain, construct artificial brains and make more effective use of our own brains. The breakthrough will be at least as momentous as the Industrial Revolution and the current Information Revolution. It will alter our lives in far-reaching and fascinating ways," he enthuses.

Computational science is a new field, and using it to map the brain – currently a section of the mouse brain, whose genome is incredibly similar in its function to the human brain.

"Many medications for humans, including some for depression, Parkinson's and Alzheimer's, have been developed on the mouse model," he continues. "The mouse is better than the rat, as the genome replicates faster and is better understood." Neurocomputation is a combination of new approach to learn more about the brain.

"If you looked at brain function as just a mechanical phenomenon," he says in an interview in his Silberman Institute office piled with papers and journals, demonstrating his points on a laptop with a screen full of stains, "you would get just a description but not a real understanding."

Einstein had a moustache and wore a business suit, while Segev is clean shaven and wears a brown leather jacket, denim shirt, sports shoes and casual beige-green trousers. But with his halo of graying hair surrounding his head and his untidy office, one can't keep wondering whether the quintessential Jewish physicist would feel at home in this office, at the university he helped found in Jerusalem 90 years ago.

"I am a theoretician. The brain is a physical system, thus many physicists have come into the field of neuroscience. With the complexity of the brain and the many levels of descriptions from genes to electrical wiring connections, we needed a new multidisciplinary approach," Segev says.

"In the past, we didn't have such an integrative attempt at understanding the brain – until Bert Sakmann [the German cell physiologist who shared the Nobel Prize in Physiology or Medicine with Erwin Neher in 1991 for their work on the function of single ion channels in cells] came and said he has plenty of anatomical and physiological data about the brain. But he didn't know what to do with all this, how to connect it and make some functional sense of it. So it was a turning point for me when I was working on individual nerve cells – and thanks to him switched to the simulation of a cortical column in the mouse brain."

Cortical columns in the cortex of the mammalian brain – each of them the size of one cubic millimeter and containing about 10,000 highly connected network of nerve cells each firing away its electrical signals like machine guns in tiny fractions of a second – are the basic units of brain function, says Segev. The cortical column is a functioning unit with each neuron connected to 10,000 others, creating close to a billion synaptic connections. If combined, all the neurons and their tree-like processes – axons and dendrites – in a single column would be four kilometers long. As the human cortex contains about one million such columns, all the neuronal fibers in the brain could be wound around the Earth many times, he calculates.

Segev credits Prof. Henry Markham, a Weizmann Institute graduate who serves as project director of the Blue Brain Project in Lausanne and coordinating work on brain circuitry and visualization, as being “much more visionary than I am.”

Markham, Segev says, wants to create a brain research center in Geneva that is the size and has the impact of the city’s CERN, the European Organization for Nuclear Research, which uses its huge particle accelerator to study fundamental physics.

Markham, for example, is working on a cortical column that involves the touching system; this best-known cortical column that processes the sensory information arriving from a rat whisker that, when in contact with something, gives the rodent the ability to navigate in the world even in the dark. Each single whisker has a connection to a particular column in the mouse cortex so that all the sensory information from this whisker is processed first in this particular column.

Another sensory system is the primary visual area that resides in the back of the skull. There, too, individual columns are responsible for specific visual functions such as responding to a particular angle (say 45 degrees) in the visual world. Indeed, the nervous system in mammals never relies on one single nerve cell for any particular function; rather a whole network of neurons does the job as an group. Now that Segev’s center has simulated in the Blue Brain supercomputer one whole cortical column, it can use it as a model for simulating others automatically, just as a polymerase chain reaction (PCR) machine used by molecular biologists can amplify copies of DNA pieces across several orders of magnitude.

The cortical column mechanism, Segev says, accepting the suggestion, is like a multiple-lens fly eye that melds a large number of images into a single composite. When the neurons in the column record and process the message from many other neurons and then another part of the brain puts all of them together and a whole scenery (visual, auditory) emerges there. In lower animals such as a fly, however, when one cell or small group of cells is destroyed, there is no replacement.

Fortunately, in mammals and especially humans, there is a lot of redundancy, so if some nerve cells are damaged, nothing happens. This, declares Segev, is very different from dependence on a single computer cable that, if severed, stops the machine from working altogether. Thus, when his science teacher in school told him that only a 10th of his brain’s neurons actually functioned, he was wrong.

“We know that all neurons in the brain operate electrically and chemically all the time under all conditions; yet, in terms of the brain’s capacity to learn new tasks, we use only a tiny part of it. Indeed, due to the inherent redundancy and the huge number of cells and synaptic connections in our brain, it is possible to embed more and more information without losing the existing information. Our brain capacity is huge!” Segev says.

But all this electrical firing requires energy, so the brain consumes about a fifth of all energy (calories) that our whole body consumes, he continues, even when we are asleep.

Simulating such columns means that you have to have a mathematical description of the electrical activity of each type of cell, which fires its own “electrical signals very specifically. There are 40 or 50 different types of cells, says the Jerusalem neuroscientist, “each with its own ‘electrical music.’ This music is composed from a series on brief (thousandth of a second) spikes whose magnitude is one-tenth of a volt.”

After having such models, one needs to model mathematically the connection between neurons (called synapses) and then connect 10,000 nerve cells and billion synapses exactly as they are in the mouse brain. One can thus replicate in details the cortical column of the mouse. The spike appears and then

disappears like fireworks, which can be translated in a bar-code or Morse-Code-like image. The spike itself is similar in a human brain and in a cockroach's brain or any other creature with a nervous system.

"We are looking for a generic, universal signal that is relevant to the brain in any mammal," he says. The Blue Brain Project will "change the way brain science is done. Unlike molecular biologists, brain scientists didn't save the actual data on each neuron that they accumulated over the years. Today, I can read papers on data, but not study the data itself. There is no human brain database (or complete mouse database) in the world, but with the umbrella provided by the Blue Brain Project, we could start comparing new information to what was already saved. So the Blue Brain Project forces participants to save their data in a standard format," Segev says.

The move from simulating the brain and treating malfunctioning neurons will not be extraordinarily long, says Segev. Markham is especially interested in brain disorders, particularly autism. "He has a line of 'autistic mice' with a pharmaceutical component that if found in high concentrations in females during pregnancy is likely to cause autism in the offspring. So he has been injecting it into pregnant mice. We plan to compare the cortical columns of normal and autistic rodents. As autistic children suffer from great sensitivity to stimuli, we think it is likely that the problem derives from specific brain mechanism that results in a hypersensitivity (barrage of electrical activity) of the cortical column in response to sensory input. We are trying to simulate this hyper-excitability. If we can see what goes wrong in the column, maybe we could repair it with medication based on our findings. I think patients could benefit in only a few years if we can prove by our computer model that a drug based on our simulation works is indeed effective."

If there is no animal model of a particular disease, the disease cannot be tackled in a systematic and deep way; the Blue Brain team will provide such a new simulation-based medical approach, he adds. In the future, a complete model of the animal brain will mean none of them has to be killed to examine its brain, Segev notes. At present, there is no schizophrenic or mouse model, but there is one for depression and another for Alzheimer's, epilepsy and several other neurodegenerative diseases.

Segev outlines several new "buzz words around the world" related to his field that will undoubtedly further push improved understanding of the brain. One is "connectomics."

"If you want to see the connection – synapse – between two nerve cells, you can't do it with a regular microscope. You must slice the cells thinly and use an electron microscope. Israel is not involved in this huge project, as the technology is too expensive for slicing the whole brain and then reconnecting the whole network in three dimensions. At Harvard, scientists have managed to stain the brain of living animals into a rainbow of 99 colors (the Brainbow technique) – this will facilitate the connectomics project as the brains of these molecular-engineered mice are glowing with colors rather than the gray matter's their natural color. Using the Brainbow, we can now observe that when the mouse learns something new, the researcher can see a new synapse being created in the living brain in real time."

Then there is optogenetics, initiated by Stanford University scientist Prof. Karl Deisseroth, in which single neurons in the brain can be turned on and off like light bulbs by adding the DNA of microbial proteins sensitive to light. Optic fibers implanted into the brain could thus control genetically and very specifically targeted brain cells within neural circuits, possibly leading to treatments for various neurological diseases such as epilepsy or retrieving sensitivity to light for age-related macular degeneration that causes blindness.

"The same molecule, rhodopsin, that enables our eyes to detect light can be embedded it into the genome of mouse," explains Segev, "the brain cells become sensitive to light. So when laser light shines on them, it activates a group of cells and enable us to uncover the function of these cells. This is a real revolution."

It is possible that specific brain regions of Parkinson's disease patients could one day soon be injected with a virus that carry the DNA that codes for rhodopsin and optic fibers could be implanted to enable to activate these regions electrically using light, and thus repair their function and ameliorate this devastating disease.

Segev refers to himself and all human beings as a "purely physical machine that can generate all the beauty of feelings and creativity. My role is to understand how this machine generates all these amazing Human things and what happens when the brain is sick. I have become very optimistic in the last few years. There has been exponential growth in the field. I never thought even a year ago that one could activate even single nerve cell in the living brain with light, not to speak about specific networks of cells. But it can be done and we do it as a community of scientists together. I can't predict what will happen even in a year because the speed of change is so huge. But there will certainly be serious ethical issues. The question is how much we want to invade, improve or change the brain. If we can manipulate genes, we can manipulate the brain."

While neuroscience is flourishing – and the 21st century has already been called the "Century of the Brain" because treatments will be needed for the aging population whose brains start to malfunction when they are old – Segev worries that the natural sciences could be overpowering.

"With all respect to science, we should preserve carefully the humanities and arts. We will have to be very careful not to destroy the arts and other so-to-speak non-scientific fields. We are losing fields and courses and staffers, and the humanities are in danger of collapsing."

With robots with artificial brains processing data and do the technical work for us, mankind "will have a lot of time for thinking, creating and enjoying each other's company and the world around us," concludes Segev, noting that arts and humanities will be be needed essentially for leisure time as they, after all, provide the meaning of what we do beyond the mere survival. "Will these robots have emotions? Self-awareness? An independent will? These and other yet-unknown issues will undoubtedly be our central concerns in the 21st century. This much is clear: We are on the brink of a great adventure."

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