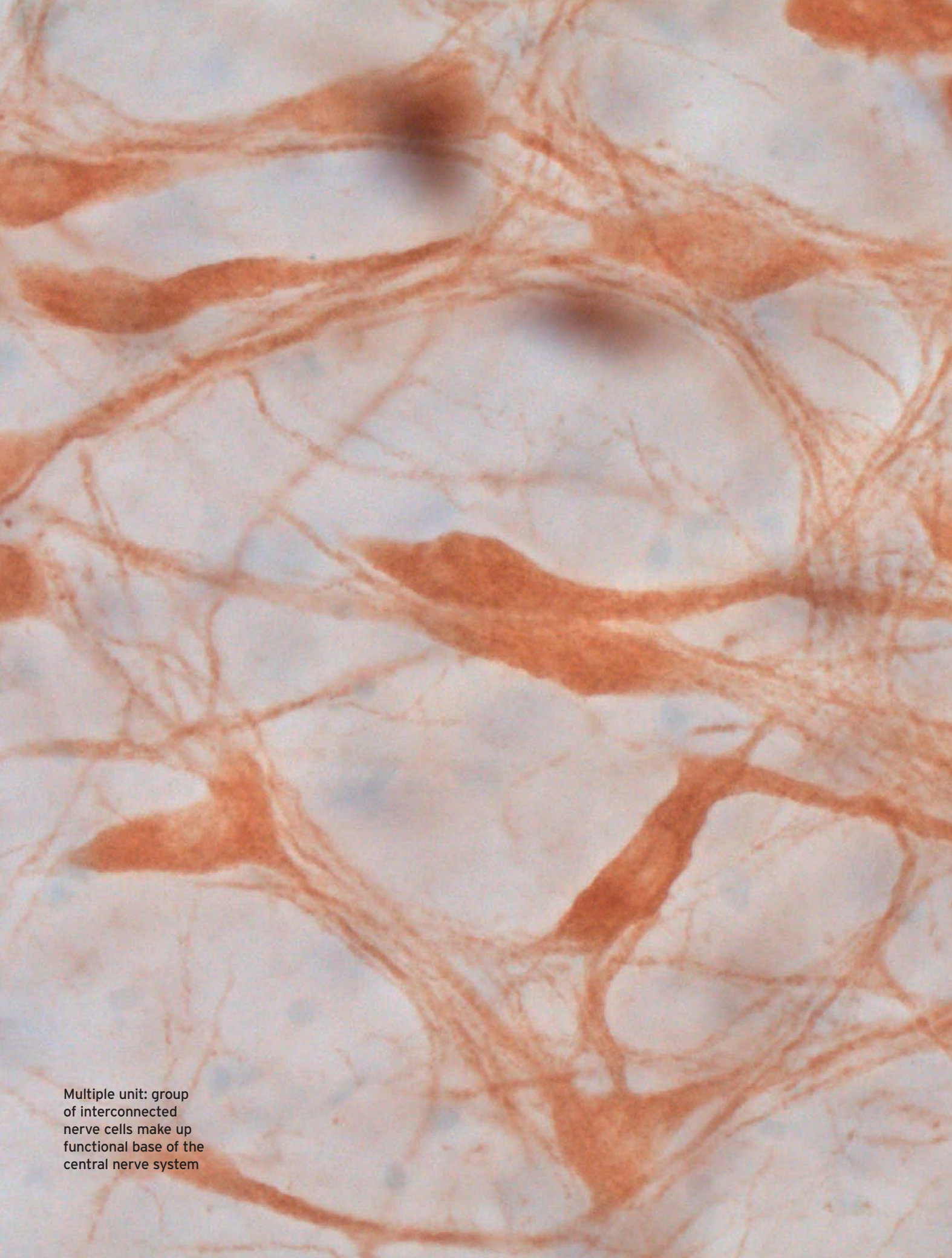

Multiple unit: group of interconnected nerve cells make up functional base of the central nerve system

RITA SINIGAGLIA-COIMBRA/UNIFESP

NEUROSCIENCE

Connection without frontiers

Cutting edge experiments with the brain travel from Duke University to Natal, along with the will to help science transform needy communities

MARILUCE MOURA, FROM DURHAM AND NATAL

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Yes, it is a dream. Or rather, a transposition to the real world. And nothing seems to be more in tune with the spirit of someone who has tried insistently, for two decades, to capture and to decode in the brain the almost invisible signals of the connections between thought and movement, intention and action, desire and realization. The name of this dream that is beginning to materialize with bricks, cement and high-level professionals in the Brazilian Northeast is the International Institute for Neuroscience of Natal (IINN). Its dreamer-in-chief is Miguel Nicolelis, 45 years old, a respected neurobiologist from Duke University, born in São Paulo, who in 1984 graduated as a physician from the University of São Paulo (USP), and is known above all, despite the important contributions he has made to basic neuroscience, for his advanced experiments with neural microelectrodes implanted in monkeys that, amongst other results, may lead to the development of prostheses for human beings, such as artificial arms and legs, that is, robotic limbs with movements commanded directly by the brain. Which is to say, by thought. Or by will. To prevent injustice, however, let

JIM WALLACE/DUKE UNIVERSITY

Action at a distance: Nicolelis trained night monkeys to move a mechanical arm using the power of the brain

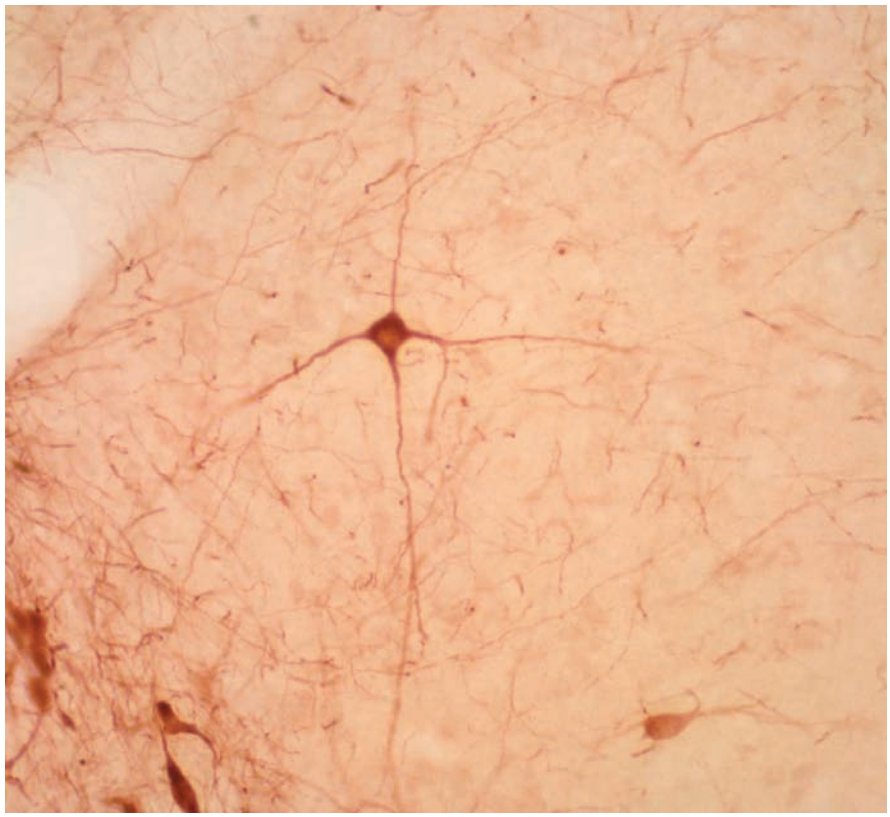
Brazilian team at Duke thinks up cutting edge research linked to social action

us include right away in the category of co-dreamers from the institute, two of Nicolelis´s colleagues: Sidarta Ribeiro and Cláudio Mello.

Imagined from a distance since 2002, inside a laboratory that had expanded vigorously to its current 1,200 square meters at Duke, in Durham, North Carolina, this institute began to operate in the middle of last year. At this moment, it occupies a rented building of 1,500 square meters in a simple street in the capital of Rio Grande do Norte, very close to the Viasul shantytown, while the more ambitious and solid forms of its own premises are going up on the campus of the Jundiaí Agricultural School, which belongs to the Federal University of Rio Grande do Norte (UFRN), in Macaíba, a small city some 20 kilometers from Natal. Note that Macaíba has no more than some 60 thousand inhabitants, while Natal is around the 800 thousand mark. Last January, in the midst of the bustle of the workmen in three different buildings in the institute under construction on the campus, the expectations were high that part of these installations could be inaugurated during the 2nd Symposium of the International Institute for Neurosciences of Natal, from February 23 to 25.

There are three buildings, let it be explained, because one is intended to be the project's Mother and Child Health Center, another to be the research center itself, and the third, a community education center. From that, you can already perceive that Nicolelis and his closest companions are thinking of cutting edge research linked to social action, and they make no secret of that. So much so, that in the waiting room of the IINN's present building, which also houses the Alberto Santos Dumont Association for Supporting Research (AASDAP in the Portuguese acronym), a notice on the wall advises visitors that this Civil Society Organization of Public Interest (Oscip in the Portuguese acronym), created on April 17, 2004 precisely to make the institute viable, "has as its objective the management of its own and third party funds for the implantation of social and scientific research projects". It goes on: "It is based on the concept that cutting edge science can, in developing countries like Brazil, act as a powerful agent for the social and economic transformation of communities located in needy regions of the national territory".

The first of the institute's buildings that the visitor coming from the state capital sees in Macaíba, on the campus's access road, on the right, is the health center. Some 500 meters further on, practically at the entrance to the campus, the research center appears. And further on, the future installations of the community education center appear. A profusion of noticeboards in front of the works advises the visitor of the political and financial support for the enterprise: the federal government is represented by the Ministry of Health and the Ministry of Education, through the Council for Advanced Professional Training (CAPES). Duke and UFRN appear on the noticeboards, as does the municipal government of Macaíba. What does not appear are the individual donors, like Lily Safra, the widow of banker Edmond Safra, who at the end of 2006 gave the project a sum that, at her request, has not been revealed , but that, according to Nicolelis, is the largest private contribution ever intended for a research venture in Brazil.



RITA SINIGAGLIA-COIMBRA/UNIFESP

In Durham, the group wanted to test whether monkeys could learn to decode – to read, shall we say – the message sent to them in the form of electrical microstimulation and associate it with a movement

Let us temporarily leave Macaíba to return to the beautiful campus of Duke, which occupies fifth place in the ranking of the most respected research universities in the United States. It was a rather cold late fall afternoon, on November 17, 2006. In one of the buildings in the biomedical area of the campus, in its large, reasonably organized room, divided into two areas, Nicolelis looked happy with the presentation made a few hours ago by the doctoral student under his supervision, Nathan Fitzsimmons, to qualify for his thesis. "In our specialization, everybody has to date managed to read signals that come from the motor areas of the brain. Except that when you move a robotic arm, you have to get signals back to understand where it is touching. And what we have managed, what he found, was basically the formula, an algorithm for sending back signals to the brain, in a sensorial feedback! It was a very good presentation", he comments.

Attention: it is very recent developments in the research with cortical implants of electrodes in mice and monkeys that he is commenting on. In this case, the work was with owl monkeys, or night monkeys – two little female monkeys, to be precise, Thumper and Pocie, as Nicolelis tells with wit in his blog on Globo Online. They are one of the models closest to man, and the results could be of utmost importance, in terms of application, precisely for the dreamt-of future prostheses commanded by the brain. Furthermore, in terms of basic science, they could add further information about how learning effectively produces microanatomic transformations in the brain. "In short, the same electrodes used to record electrical signals from the motor areas have allowed us to pass a digital message directly into the somesthetic cortex, the superficial region of the brain that identifies stimuli applied to the surface of the body, to see whether the brain learns to understand what is coming", the researcher explains. In other words, Nicolelis and his group wanted to test whether monkeys would learn to decode – to read, shall we say – messages sent to them in the form of electrical microstimulation, and associate them with a movement. "We went from something very simple, with a fixed pat-

tern, to another more complex, mobile, with a space-time dimension."

In a first experiment, the animals should learn to associate arbitrarily the electrical stimulus in the cortex to a movement to the left or to the right that makes it possible for them to find food kept in compartments on one side or on the other. For example, if the electrical stimulus appears, it ought to go to the left, and, if not, to the right. They took 40 days to learn. In the following experiment, with a more complex pattern, with time variations, surprisingly, they took only ten days. "Probably because they generalized the information, and that gave them more facility for learning", Nicolelis observes. Afterwards, when the researchers reverted the pattern learnt, each monkey learnt the new pattern even more quickly: first, in four days, the simplest pattern, and in three, the most complex. The experiments continue, and, last November, the researchers were starting to use 16 electrodes in the experiment, instead of the four used up until then.

In the neuroscientific literature, according to Nicolelis, the commands regarding movement are normally attributed to introspection, when to stop or to move is determined inside the brain itself, and, in a pattern that the researcher calls second degree, to the external environment. So it is something cultural, learnt. One example is the immediate impulse of all motorists to stop the car when the traffic light turns to yellow, announcing that the red light will be next. "In Brazil, though, something very peculiar happens, which is accelerating the car to go through on the yellow light", the researcher jokes. Amongst primates, and perhaps other mammals, stopping or going may also be determined by a verbal command "From that, I called it 'a close encounter of the third kind' a message comes from an artificial system, a digital command directly in the brain, which is arbitrary and comes to have a meaning", he says. This abstract message connected with a motor command "produces a microanatomic transformation", he adds.

And why is Nicolelis sure about that? "We saw, with different algorithms sent off at the same time, that over the period of learning, the process of the arbitrary message would transform itself into a clear motor command. For the first time, we were successful, at the same time that we were stimulating the somesthetic cortex, in reading the signals produced in another area of the brain, the motor area, and in decoding with precision the animals' intentions, the movement that they were going to make, before performing it", he details. This with a time difference of 100 to 200 milliseconds.

In this field, incidentally, Nicolelis's team has, at this point, begun even more exciting experiments with owl monkeys, something that now appears to belong frankly to the realms of science fiction and that he calls a "close encounter of the fourth kind". There are some impressive results, but he prefers to remain cautious and not to reveal anything before more certain confirmations.

GIOVANNI SÉRGIO

GIOVANNI SERGIO

Concrete dream: workmen erect research (*above*) and community education centers

In the IINN in Rio Grande do Norte, at this moment there are 12 researchers working under the command of 35-year old Sidarta, the institute's scientific coordinator, as well as a floating population of visiting researchers. On the afternoon of January 11 last, for example, there was to be found amongst them Eduardo Schenberg, a pupil of Koichi Sameshima, a neurologist from the Syrian-Lebanese Hospital, in São Paulo, an institution with which the IINN maintains a collaboration agreement that is now showing interesting results, particularly in studies of Parkinson's disease. The installations in the institute's rented premises, despite the intention to move a good part of the laboratories to the new premises in Macaíba in the short term, are well prepared for an important part of the research with electrodes – the rodents' vivarium and the surgical center, for example, seem to be first class. And the building also has adequate rooms for experiments on human beings that are part of Sidarta's line of research on sleep and memory. Also taking into consideration employees from the administrative area, there are 20 persons distributed between the institute's main building and a second building aimed at community health of the local population, nearby.

Sidarta graduated from the University of Brasilia (UnB) in 1993, took a master's degree in biophysics at the Federal University of Rio de Janeiro (UFRJ) and a doctorate in cognitive molecular neurobiology from Rockefeller University (1995-2000), and was finally brought into Nicolelis's laboratory at Duke in 2000, first as a postdoctoral student and next as an associate researcher, and he looks quite naturally upon his work as IINN coordinator.

On this point, let it be said that one of the criticisms of the IINN enterprise from part of the Brazilian neuroscientific community is precisely the way he conducts the coordination, which some see as a sign of the closing up of Nicolelis's group, instead of the expected opening out and interaction with various other neurology groups in the country. "Sidarta is a brilliant researcher, extremely promising, but the choice of him as scientific director was frustrating, because it does not appear to have been the result

This dream began in Juqueri in the 1920s or 1930s. The Juqueri, in Franco da Rocha, São Paulo, tried to be at the outset a cutting edge research center

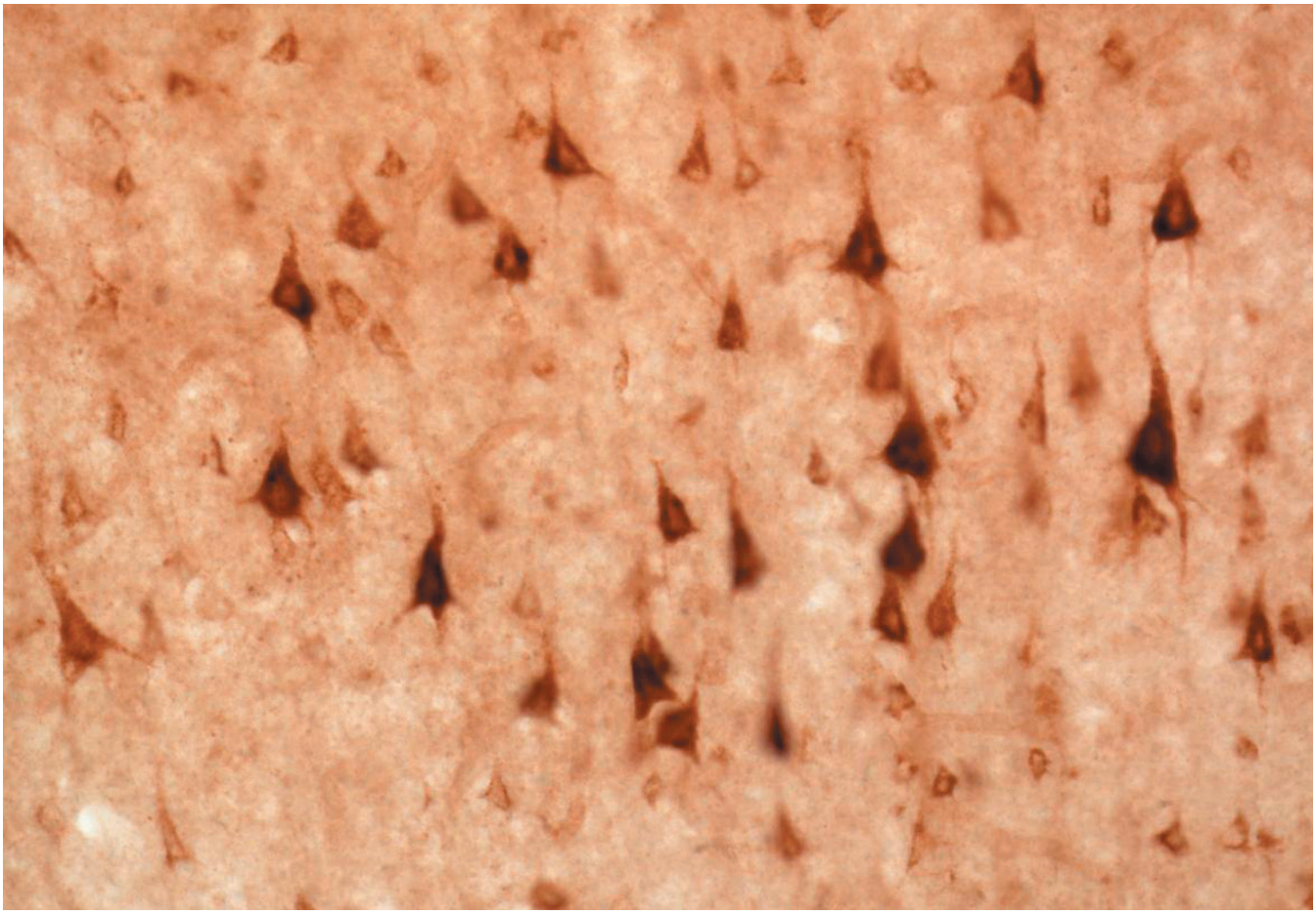
of a selection process with clear bases. The institute is now beginning to select researchers, postdoctoral students, but it all sounded very restricted at the outset, and that was one of the criticisms raised at the 1st Symposium of the IINN, in 2005." The comment is by Luiz Eugênio Mello, pro-rector for postgraduate studies at the Federal University of São Paulo (Unifesp) and a specialist in neurophysiology, with respected contributions in the area of epilepsy. Mello, until recently a scientific advisor to FAPESP, makes clear his admiration for the work of Nicolelis, whom he classifies as "a brilliant scientist, at the forefront of modern science that advances towards the area of application". And he admits that now the quest for interaction of the team with other Brazilian scientists is expanding. So much so that he himself is taking part in a project of cooperation with the IINN coordinated by Iván Izquierdo, of the Pontifical Catholic University of Rio Grande do Sul (PUC-RS), which also involves the group of Marco Antonio Máximo Prado, from the Federal University of Minas Gerais (UFMG).

"I think that what stirred up the community a lot at the first symposium was the fact that the group presented itself as the pioneer and founder of neuroscience in Brazil. So each one of us wondered whether what we had done in the last 30 or 40 years was not worth anything", Mello comments. Incidentally, for him, it was possible for the IINN enterprise to happen in Natal also because, some 30 years ago, a neuroscience group was set up at UFRN, led by Elisaldo Carlini, from Unifesp. Without that, it could have been, as he understands it, any other city. Actually, behind the disputes and jealousies that are understandable in the university community, there seems to be a certain fear relating to the scarcity of funds for research in Brazil. "As resources are finite, Nicolelis's group is well connected politically and very competent scientifically, there really is a certain fear in the air when an enterprise vaunted as collective proves to be centralized in the process of defining who goes there."

What perhaps few may know is that Sidarta considers himself, not without reason, as co-responsible for the idea of the institute. And Nicolelis leaves room for him to assume this condition. Accordingly, to the question posed in his room in Natal about whether the institute is a dream of Miguel Nicolelis with which he has contaminated many people, Sidarta replies that, in actual fact, it is not quite like that. "This dream begins in Juqueri in the 1920s or 1930s. Juqueri, in Franco da Rocha, São Paulo, tried at the start to be a cutting edge research center, and to this end brought together neuroscientists, doctors with a psychoanalytic influence... As an undergraduate, I was given this story by my neuroanatomy professor, Marcos Marcondes de Moura, who went so far as to be the director at Juqueri. He used to talk a lot about this, about the Juqueri's research program for understanding mental illness, the brain bank etc. Both theoretically and experimentally, they had great ambitions", says Sidarta. And his conclusion is that he was contaminated by Marcondes with the idea of doing cutting edge science in Brazil in this neurological area.

"When I went to the United States, I had this idea in my head. And I went about passing it on. I passed it on to Cláudio Mello, who was also from Brasilia and was my supervisor at the Rockefeller. Then we started to create a group of people inside the Rockefeller who were thinking about this idea. And that

GIOVANNI SÉRGIO



RITA SINIGAGLIA-COIMBRA/UNIFESP

Creator and creature: conceiver of the institute in Natal, Sidarta analyzes action of neurons during rodents' sleep

reached Torsten Wiesel, the President of the university, who was thrilled", he details. When he got to know Nicolelis, in 1998, and became enthusiastic about his work and his methods, Sidarta talked to him about the idea of the institute.

"Miguel was also enchanted, but at the beginning he was very well established at Duke. He was certainly the Brazilian neuroscientist with the greatest impact worldwide, a full professor with an excellent laboratory, two in fact, with plenty of finance." So his reaction, according to Sidarta, was positive, he thought that the idea was very good. And because of his political commitment (his biography includes his struggles as a militant for the re-democratization of the country in his youth and his presence amongst the founders of the Workers' Party, the PT), he offered to help. At that moment, they were thinking about creating a cutting edge institute, in a beautiful place that would attract people from all over the world, where they would do research directed by the problems, and not by the techniques.

"It was a very romantic idea, even with access to the forest to study animals in the wild ", says Sidarta. Accordingly, at the beginning, Nicolelis's help for the project was to lend his prestige to make it viable. "However, he himself went on getting more and more enchanted with the idea, and at a certain moment really brought something new to the project: giving it a social mission", he says. So the idea, until then merely a scientific one, "with Miguel incorporated this other dimension. That was at the end of 2002, beginning of 2003, in the small hours, soon after Lula's victory for the presidency". And with this, Sidarta goes on, "it comes together with a wish to bring the ludic, ethical, meritocratic and even disciplinary values of science to society, within the view that knowledge really is a liberator". But, Sidarta adds, "without the force of Nicolelis's enterprising spirit, none of this would have gone ahead".

In front of the computer in the area that he occupies on the left of his room, Nicolelis explains that the implants used in the animals in the experiments, made of tungsten and resin, are 4 or 5 millimeters in length, two millimeters of which remain in the brain. He will soon show us the neuroengineering room of the laboratory where the electrodes are built. Actually, it is always problematic when something foreign is put into the body, with one part inside and the other outside, because this facilitates infections. But one of the laboratory's monkeys has now had the electrode in his brain for six years without any problem. Nevertheless, as you have to think of the future, engineers connected to several research groups are working on the development of wireless implants, in more effective neuroprostheses, "and one of Japan's main robotics laboratories, the ATR, has decided to participate in an international effort to search for better robotic arms and a vest capable of working like an exoskeleton".

The conversation turns to the important experiments connected to Parkinson's disease, which have given Nicolelis good evidence that a principle that he has been postulating for years is right, that is, that populations of neurons, and not a single neuron, constitute the functional units of the brain. On account of these experiments, neurosurgeons from Duke recently met neurosurgeons from the Syrian-Lebanese Hospital, at a workshop in São Paulo, to train them in a technique with electrodes that gives more precise indications, in a much shorter time, about the areas that have to be removed to prevent the disagreeable symptoms of the disease. As all this is done with the patient completely awake, it is also possible to observe the patient's responses that lead to completely unexpected results.

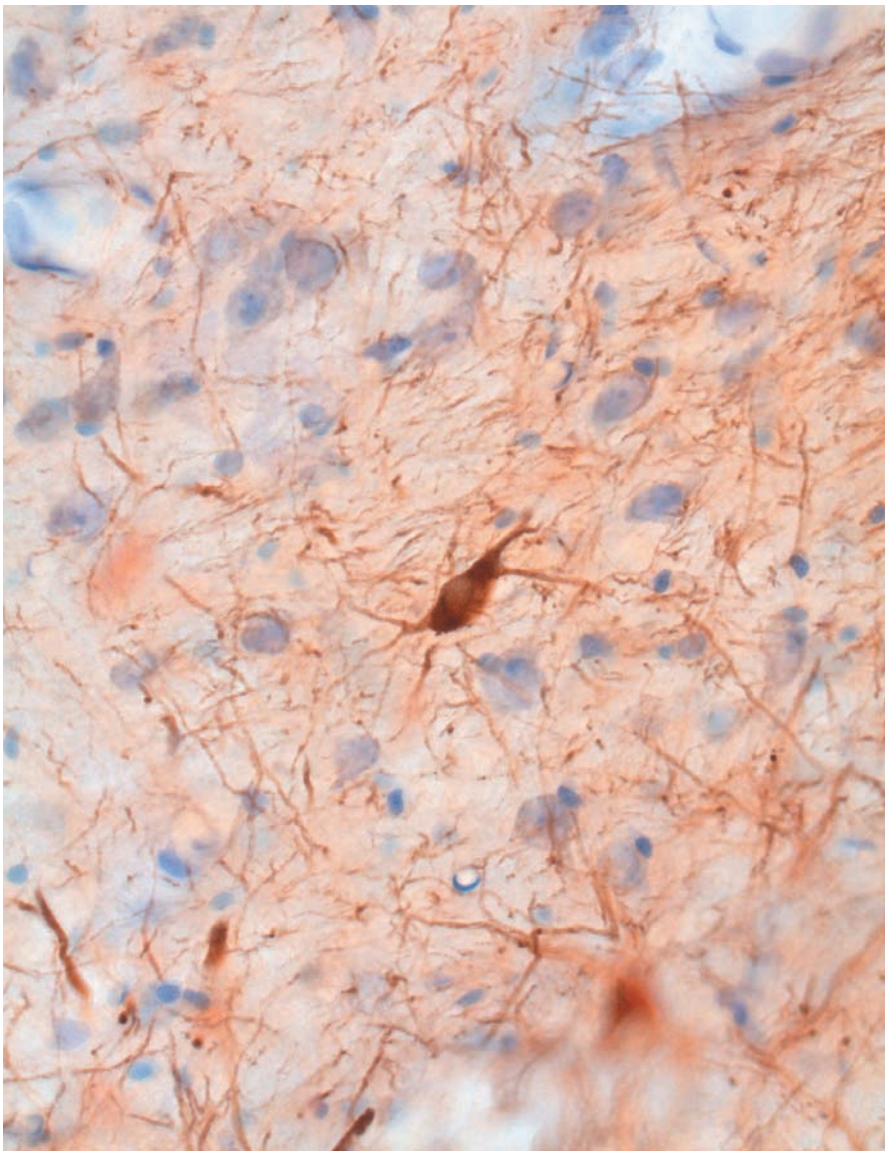
"For example, we now know that, with only 300 cells, it is possible to produce a complex motor behavior", says Nicolelis. Of course, he says, "a given number of neurons are needed to sustain any behavior, but instead of thousands, it is possible for hundreds to acquit themselves of the task". In actual fact, in a simplified way, what Nicolelis has proposed is, first, that the functional unit of the brain is not the neuron, but a population of them. In second place, that this population does not always have the same elements, but their constitution changes every moment, that is, certain neurons are summoned at one moment for the task of moving an arm, and, later on, others, not the same ones, may be called on to repeat the task. That is why you can have traces of motor behavior in areas of the brain that, in principle, have nothing to do with movement. "In other words, the system is distributed, flexible, and not rigid", he sums up. Nevertheless, he emphasizes, "the concept of distributed code does not eliminate the concept of specialization. One does exclude the other".

One proposal that all this raises is that the human brain perhaps has millions of neurons like a sort of potential reservoir to meet, at any moment, the need for these cells to carry out each behavior. Moreover, in the absence of specialized cells, others may handle the task.

This notion of populations of neurons as a functional unit of the brain sounds "very sensible and very intelligent" to neurologist Iván Izquierdo, who, just like Nicolelis, is among the most quoted Brazilians in scientific literature. "It is obvious that, in some aspects, the cell is a unit, but not from this functional point of view", he says. Much respected for his studies of the memory and mechanism for its consolidation, Izquierdo is at this moment concluding an analysis of his collaboration with the group from the IINN, for studies in neurophysiology, neurochemistry and neuropharmacology in the aged. "We are awaiting funds from the National Council for Scientific and Technological Development (CNPq) and we are going to work with an animal model: transgenic mice." He says that he is rooting for the institute in Natal to do well and to be able to transform itself into an important center to attract scientists from the south and center of the country.

Luiz Eugênio Mello also finds the idea of neuronal populations interesting. "It seems to make sense, but it is difficult to have conclusive demonstrations of this, not least for the very question of floating populations." He imagines a model where floating neurons exist, but at the same time are related to a restricted, specialized and always active nucleus. As to the real application of robotic

A principle that Nicolelis has been postulating for years is that groups of neurons, and not each neuron, constitute the functional units of the brain



RITA SINIGAGLIA-COIMBRA/UNIFESP

Floating populations: distinct groups of nerve cells may control one and the same action at different moments

arms and other prostheses, he says that he sees a lot of future "if we succeed in overcoming some obstacles". For example, if the implant is put totally inside the head, to prevent infections. If it can be activated without a wire, "with radio waves, for example, as we are trying to do".

Miguel Nicolelis shows an optimistic video about the institute, very close to the River Potengi, a tributary of the Jundiaí. When asked why in Natal, he replies "because if we manage to do it there, it becomes clear that institutes like this can be installed anywhere in Brazil". On the walls near his computer, there are many magazine covers, from *The Journal of Neuroscience* to *IstoÉ* (a weekly news magazine in Brazil), from the most specialized, scientific ones, to the most general. On the walk across the campus to reach the other laboratory, in the midst of the now intense cold at the end of the afternoon, he talks about the book, more for laymen, about the history of his experiments, that he needs to finish for publication at the beginning of 2008, and of another two, more scientific. "What I want is to present a more comprehensive theory about the interaction of the brain with the technology that our culture is creating. That may perhaps help to explain a series of phenomena that are not restricted to one brain, but relate to multiple brains interacting. And I advocate that perhaps some social behavior may be defined in the likeness and similarity of how brains naturally work."

It is a daring idea. About investments in Duke, Nicolelis says that about US$ 40 million is invested in his two laboratories. And in Natal? Certainly, the figure of the originally estimated US$ 25 million has now passed. And, running one of the 20 international groups in cutting edge neuroscience, he dreams of a virtual institute of the brain, integrated by many units scattered all over the world, a horizontal

Science produced in collaboration, independent of geography, based on the interaction of talents. A sort of archipelago of knowledge, combating the poverty around it – the neolithic misery, as Sidarta says. He dreams of other research institutes in the Northeast. Really dreaming, according to Sidarta's research hypothesis, may perhaps be to simulate possible futures based on a remembered past. ■