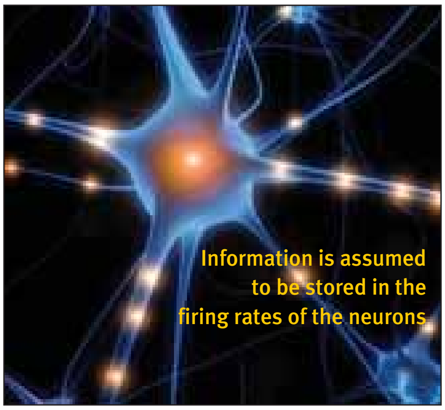
Computational Neurobiology in Turin

"Not just Running a Specific Programme"

Billions of neurons are involved in the complex network mechanisms leading to memory formation. Nevertheless, theoretical physicist Riccardo Zecchina and his team in Turin were able to provide some explanations as to how neurons might store information by applying an "extremely simple algorithm".



Information is assumed to be stored in the firing rates of the neurons

Memory and learning are essential processes in life. Not only for embarking on successful careers, but also for learning banalities such as walking, talking and facial recognition. The mechanisms leading to the remembrance of facts are complex. Neuroscience teaches that memory and learning produce changes in the brain, for instance in the nervous circuits responsible for perception and movement control. And although the brain consists of billions of neurons, the individual changes occurring within cells are thought to be relatively simple and unique.

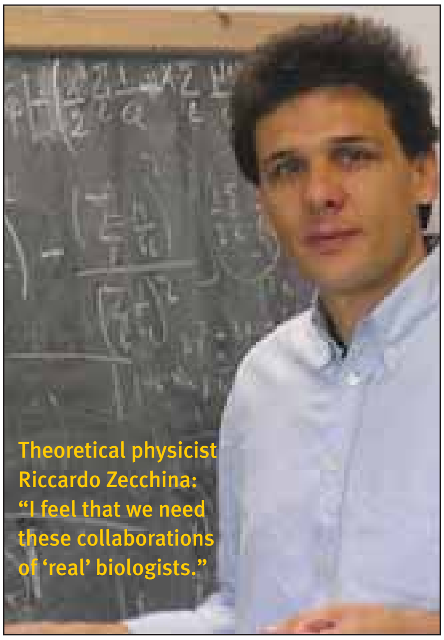
The mechanisms involved in learning are what Riccardo Zecchina from the Department of Physics at the Politecnico di Torino, Turin, Italy, is interested in, but from a more theoretical than practical-biological standpoint. The theoretical physicist focuses on computational biology issues, using modelling and simulation of biological systems to get a deeper understanding of, for instance, how the storage of information in the neuron can be achieved. "We aim to find meaningful algorithms by which we can describe complex biological processes, by which we hope to get a more general insights into them," explains Zecchina.

For about three years Zecchina has worked on computational problems arising from biology. "I have been studying learning problems before, but at that time, I did that in really artificial systems."

A complicated problem...

From a biological standpoint, learning and memory are believed to be achieved through forms of synaptic plasticity. Long-term potentiation and depression, the increase or decrease in the excitability of a neuron to a particular synaptic input, respectively, are known to be processes involved. Yet, how synapses and neuron-networks change their efficacy and how they can maintain these changes over time to learn patterns, for instance, still remains unclear. A fairly complicated problem from a computational point of view, thinks Riccardo Zecchina. "Well, today, synapses are thought to behave somehow like 'noisy switches', having a finite number of stable states rather than a continuum of states", he says. Binary synapses characterized by two stable states, inactive or active, seem to be reasonable models in this respect, as they are simple devices that are relatively robust to noise and hence could preserve memory over a long time, Zecchina continues.

In several existing neural network models of memory using binary synapses, learning occurs in an "unsupervised" way. This means that the synapse transits between the two states of no or high efficacy induced by pre- and post-synaptic activity alone. "But in most of the learning protocols that have been studied in the past the binary synapse is bad or even unable to store information," says Zecchina.



Theoretical physicist Riccardo Zecchina: "I feel that we need these collaborations of 'real' biologists."

Therefore, Riccardo Zecchina and colleagues focus on a supervised learning scenario, in which an additional "teacher" or "error" signal induces synaptic modifications.

The simplest prototypical model in which this type of learning has been studied for decades, is a "perceptron" of neurons, describes Riccardo Zecchina. This artificial neural network has to perform a set of input-output associations, meaning that it has to learn to classify correctly the input patterns into two classes. "It is a most simplified thing, just a threshold unit with a lot of synapses coming in." However, learning with such a simple device is known as a so-called "computationally NP-complete hard problem", meaning that although theoretically possible, efficient algorithms have not been found so far. Even for random patterns the problem appears numerically extremely difficult to solve.

"Nevertheless, in everyday life the neuro-system in fact solves this problem," Zecchina points out.

... simulated by a simple algorithm...

He and his team addressed this problem by applying an established algorithm to the perceptron system, a binary neuron together with its presynaptic inputs. This approach has already performed quite well in solving efficiently the learning problem. In addition, each synapse was endowed with a finite number of "hidden" states, which may correspond to the state of the post-synaptic protein interactions. "However, the algorithm we used has a number of biologically unrealistic features", admits the 44-year-old. In order to make the system biologically meaningful and to satisfy a set of necessary requirements the researchers successfully modified the existing algorithm. "In the end we found an extremely simple algorithm which is just a slight modification of traditional learning rules that have been studied since about 40 years", says Zecchina of their recent results (*PNAS* 2007, 104, p. 11079). "This algorithm is now able to store a lot of information and can thus efficiently achieve a large number of patterns learned per synapse, and the process is very simple and fast!"

... with a deep theory behind it

In the model that Riccardo Zecchina and Co. studied, information is assumed to be stored in the firing rates of the neurons. "Our next step will be to consider a so-called spike response model." This is a generalized integrate-and-fire model, where special functions display the action potentials, the reset and refractory periods of a neuron, and the neuron response to input spikes. Zecchina finds it fascinating to contemplate how learning can take place when both models are considered. "That would tell us something about what kind of information neurons are exchanging and about the information content of single spikes."

Doing theoretical science in this context predominantly means designing a model that covers realistic constraints, as Riccardo Zecchina understands it. "We don't want to look for the 'lost keys under the lamp' to problems that we invent on our own," stresses the theoretical physicist. As an expert in computational and algorithmic methods, he uses *in silico* protocols to converge the goal. "Of course, this is not just running a specific code or programme! There is a deep probabilistic theory behind it about what this code is doing." A later step would be to compare the results with the outcome of "wet" experiments obtained in the biological system to validate how relevant the produced models are for real life.

To get comprehensive insights into complex problems like learning and memory, Riccardo Zecchina feels one thing is crucial: interdisciplinary work. On the one hand, biologists would not have the background for theoretically solving these complicated problems, but on the other, the theorists would not have the background to understand the biological constraints, he explains.

"Therefore, our group consists of persons with different backgrounds. There are computational scientists, but also a number of experts in biology, neuroscientists, and also molecular biologists.“ By "our group" Riccardo Zecchina refers to the entity that results from a relatively big collaboration. "Actually, these are three research groups that assemble to just one group at the end, which is located partly at the Politecnico di Torino and partly at the Institute for Scientific Interchange (ISI) in the same town," he explains. Besides Zecchina's groups at the Politecnico di Torino and at ISI, there is also the group of the neuroscientist Nicolas Brunel, who actually works at the Centre National de la Recherche Scientifique (CNRS), University Paris V, France. A bioinformatics group lead by Martin Weigt tries to use algorithmic tools for network reconstruction from gene expression data.

Considering the biological constraints

"Essentially, we have two applied research lines, one concerns computational neuroscience and the other computational problems arising in the context of molecular biology," says Zecchina.

There are additional collaborations with groups in the States, for example with the Theory group at Microsoft Research in Redmond, where Zecchina actually spent six months on a scientific exchange.

"I feel that we need these collaborations of 'real' biologists, experts in neuroscience, and us as theorists," stresses Zecchina. "And it makes the thing interesting! We learn a lot of and from biology and neuroscience."

This is how modern science works today, intertwining different disciplines. Riccardo Zecchina is sure that "we are almost there!".

Susanne Dorn