

High Performance Computing

Case Study.

Breakthroughs in
Brain Research with
High Performance
Computing



Compete.

Council on
Competitiveness

Breakthroughs in Brain Research with High Performance Computing

Researchers at the Salk Institute are using supercomputers at the nearby NSF-funded San Diego Supercomputer Center to investigate how the synapses of the brain work. Their research has the potential to help people suffering from mental disorders such as Alzheimer's, schizophrenia and manic depressive disorders. In addition, the use of supercomputers is helping to change the very nature of biology – from a science that has relied primarily on observation to a science that relies on high performance computing to achieve previously impossible in-depth quantitative results.

To paraphrase Yogi Berra, *You can see a lot just by looking.*

With the help of high performance computers at the nearby San Diego Supercomputer Center (SDSC), researchers at the Salk Institute for Biological Studies in San Diego are engaged in a lot of serious looking at how neural communication within the brain works. What they could uncover has the potential to help people suffering from some of today's most intractable mental disorders, such as schizophrenia, Alzheimer's and manic depression.

Established more than 40 years ago by Dr. Jonas Salk, the developer of the polio vaccine, the Salk Institute conducts biological research into molecular biology and genetics, neuroscience and plant biology. The institute consistently ranks among the leading research institutes in the world. It is dedicated to the premise that basic research is truly "where cures begin." Discoveries of the principles governing cellular activity have often proven to be the basis for new and effective therapies and cures.

It is in this spirit that Terry Sejnowski, Tom Bartol and a cadre of graduate students have been studying the ciliary ganglion of chickens with the help of high performance computing (HPC). The ciliary ganglion is a mass of neurons in the ciliary muscle – the muscle that opens and closes the iris in a human or animal eye. It acts like a circuit, controlling the muscle's functions. Within the ganglion is a synapse – the communication junction point where nerve cells communicate with target cells

like those in a muscle or gland. By studying the ciliary ganglion of a chicken and how the synapse controls neural communication, researchers like Sejnowski and Bartol are gaining new insights into the neural communication pathways of the human brain that could lead to new treatments for serious mental disorders.

Better Drugs for Better Living

Compared to the tangled skein of synapses in the brain, the ciliary ganglion of a chicken is highly accessible, rather large and can be easily removed for study. The synapse within the ganglion has many communication release sites and a very intricate geometry, allowing researchers to conduct experiments that would not be possible within the brain itself.

"By investigating the ciliary ganglion, we have been gaining a greater understanding of the operation of synapses in the brain and neuromuscular junctions elsewhere in the body," says Sejnowski. "I think it's fair to say that every mental disease – from Alzheimer's to schizophrenia, in one way or the other involves chemical imbalances at the synapses that cause disorders in synaptic transmissions – in other words, miscommunications between neurons. Most drugs for neurological disorders are targeted at these synapses and, to some extent, are able to rebalance these synapses."

For example, drugs that are used to treat depression, such as serotonin reuptake inhibitors like Prozac and Zoloft, change the balance of neurotransmitter levels

in the brain's synapses – in this case, in the serotonin synapses. In schizophrenia, the drugs of choice act on the dopamine synapses.

“To some extent, these drugs are able to rebalance the synapse,” Sejnowski explains. “However, we really need to understand what’s going on at a much deeper, more accurate level. Once we know precisely what the problem is, we will be able to design better drugs and therapies.”

Bringing Tissue to Life

The particular synapse that controls the eye’s ciliary muscle has been under study for many years. The Salk Institute became involved when Sejnowski and Bartol read a research paper by a graduate student at the University of California at San Diego (UCSD) that for the first time described the shape of the synapse in three dimensions – and a very strange shape it was. The reconstruction of the synapse raised more questions than it answered.

“We became very curious about how such an odd structure would function in real life,” recalls Bartol. And so in partnership with UCSD, they began to build a 3-D, molecular-level, computational model to better understand the ciliary synapse. Using a program called MCell, which simulates cellular microphysiology and was developed specifically to study synaptic transmissions, they created the first computational model of the biochemical function of this synapse.

After refining the model to make it match the already known behavior of the synaptic function that had been obtained through laboratory experiments, they were ready for the next step – the Yogi Berra look and see phase. The researchers made an initial setting of the parameters (the equations used to simulate reality), ran the model on in-house workstations and then looked to see what happened. “In a sense,” Bartol explains, “we brought this little piece of tissue back to life inside the computer.”

As the ciliary ganglion began to “come to life”, Bartol, Sejnowski and their research team started adjusting the mathematical parameters to obtain more accurate approximations of its real-life complexities.

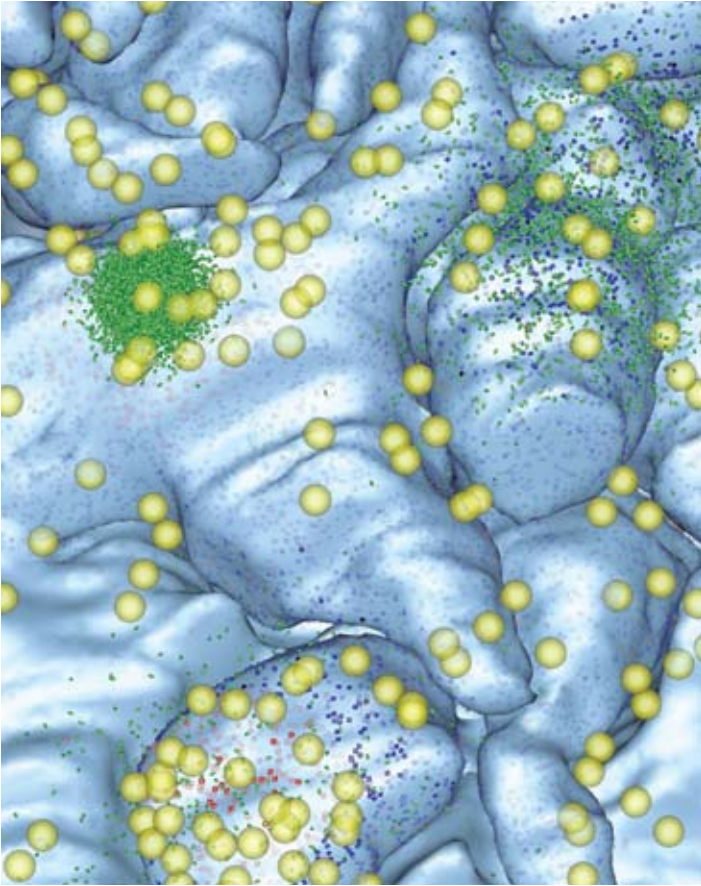
“We did what is called a ‘parameter sweep,’” Bartol explains. “This consists of making numerous adjustments to the numerical parameters used to provide an approximate model of reality. So, I have nine different parameters, and now I want to know what will happen to my model when I vary all nine of these parameters, let’s say using five different values, all independently of each other. That’s nine to the fifth power – and now we are in major supercomputing territory.”

Looking and Seeing with HPC

To handle computations of this size, the Salk Institute researchers have been using the San Diego Supercomputer Center (SDSC), one of several university supercomputing centers supported through the National Science Foundation to provide HPC capabilities to researchers across the country. Given the complexity of the current research, the Salk team simply could not run the simulations without access to the SDSC system.

The parameter sweeps and simulations executed on the SDSC high performance computer had some surprises in store for the Salk investigators. The classic view of how synapses work, derived from laboratory investigation, is that neural transmissions occur primarily in dense, protein-rich areas called active zones. But when the Salk team ran their models on the SDSC system, the results indicated that neural communication was not confined to just the synaptic active zones, but took place in peripheral areas as well outside of the synapse. This was highly unexpected and exploded the traditional thinking of how synapses work.

“It took high performance computing to reveal how limited our concept was of how synapses functioned,” Sejnowski explains. “It appears there is a second channel outside the active zone of synapses that may be used to process different types of information. While we had been aware of these “extra-synaptic” receptors, we really had no idea until now what they were for. But now we are beginning to understand that there is a completely separate mode of neural communication, perhaps going on in parallel with the synapse, which was not apparent until we ran the supercomputer simulations.” New experiments conducted by other researchers seem to support the Salk team’s unconventional findings.



Communication between neurons in the brain occurs at synapses—specialized points of contact where one neuron sends a chemical signal to its neighbor. This image shows a realistic computer simulation of neurotransmission in a chick ciliary ganglion synapse. Image courtesy of Salk Institute for Biological Studies.

“The high-performance supercomputer gives us a scientific instrument like none other that has ever existed and will lead to discoveries that we can’t even contemplate now. It is changing the way we think about the brain, and the way we think about biology in general. We are entering a whole new era.”

Terry Sejnowski, professor and head of the Computational Neurobiology Laboratory, Salk Institute for Biological Studies

HPC Impact: Changing the Face of Biology

By studying the ciliary ganglion, researchers at the Salk Institute are accumulating valuable information that can be applied to the way other synapses in the brain and neuromuscular connections work, not just in chickens, but in human beings as well. Sejnowski and Bartol indicate that findings from the pure computational research they are conducting will impact the treatment of many neurological diseases. Most of today’s pharmacological agents affect synaptic transmissions. But now it appears that there is significant chemical communications between neurons at other places in the brain and body as well, and these may be implicated in neurological and mental disorders. This revelation may open up pathways for new drug treatments.

But the benefits derived from the combination of the Salk Institute research and HPC have even wider implications.

For example, HPC allows the researchers to bring together anatomical, physiological and biochemical data and draw conclusions that are not readily apparent when these and other related disciplines are studied on their own.

“In the past, we always had to think how to simplify our models to run on the existing hardware and software,”

says Sejnowski. “Now, we are able to do things we could only dream about before. Modeling a biological system makes weather modeling seem like child’s play. But with the power of supercomputers and access to the HPC systems at SDSC, we no longer need to think about how to simplify the models – now our task is to make sure to mine all the information that is pertinent to our experiments and create the most detailed model we can. If I wish, I can run the model a million different times at a million different points in parameter space to get an extremely accurate picture of how the brain works at the molecular level. With this kind of data, we can derive optimum computer models that will allow us to make better predictions for how to design better drugs.”

Bartol points out that biology traditionally has been an observational science – a matter of looking and seeing. But like physics before it, biology is about to reach a major inflection point. In physics, Galileo and Copernicus made observations that fundamentally changed the course of science and our world view. Newton added a basic mathematical framework and defined classical physics. But with the development of the mathematics supporting relativity and quantum physics at the beginning of the 20th century, physics made a major leap forward and became the powerful predictive force that we have today.

By taking advantage of the awesome power of supercomputers, biology is undergoing a similar paradigm shift, becoming a far more quantitative science. “As soon

as a branch of science turns that corner, huge things begin to happen,” says Bartol. “In the near future, we will integrate the computational sciences and biology – in fact this is already happening at the level of molecular genetics. The next frontier will be to integrate massive amounts of data into quantitative and predictive models in ways that could not be done previously without the power of high performance computing.”

“Look at it this way,” Sejnowski continues. “The brain is the most complex computing device in the known universe. If you have any hope of being able to tease out its secrets, you need a tool that is as complex and able to track all the details as the brain itself. The high-performance supercomputer gives us a scientific instru-

ment like none other that has ever existed and will lead to discoveries that we can’t even contemplate now. It is changing the way we think about the brain, and the way we think about biology in general. We are entering a whole new era.”

The work of the researchers at the Salk Institute, combined with access to the powerful HPC system at the San Diego Supercomputer Center, is helping to move the field of biology in new directions that hold the promise of innovative treatments for brain-related disorders. Their contributions appear to be following the wisdom articulated in these immortal words of Yogi Berra: *If you come to a fork in the road, take it.*

In Brief

Key Challenges

- Find better ways to investigate the complex structure of the ciliary ganglion to learn more about how synapses function in the brain and neuromuscular systems
- Uncover information that will aid in the creation of more effective drugs to treat mental disorders

Solutions

- Create computational models of the cellular microphysiology and synaptic transmissions of the ciliary ganglion of chickens
- Take advantage of the immense computing power of the high performance computing system at the San Diego Supercomputer Center to run these models and perform “parameter sweeps” – numerous adjustments of the numerical parameters making up the simulation of the ganglion to provide the closest approximation of reality possible

Key HPC Benefits

- Allows Salk Institute researchers to run simulation programs at a level of complexity previously not obtainable by in-house workstations
- Provides opportunities for breakthroughs that would not be apparent without supercomputer simulations, such as the Salk team’s discovery of a second channel for neural communications
- Provides research results that will help pharmaceutical companies design more effective drugs to treat mental disorders
- Advances biology from a primarily observational science to one that is predictive through the use of quantitative and computational methods

Web Site

- www.salk.edu



Instead of using 100% virgin paper, we used paper that has been 30% Post-Consumer Recycled and made with 100% wind-generated electricity. We saved:

5 trees preserved for the future

1667 gal of water flow saved

276 lbs of solid waste not generated

509 lbs of greenhouse gasses prevented

3 million BTUs of energy not consumed

Environmental impact statements were made using the Environmental Defense Fund Paper Calculator.

Council on Competitiveness
1500 K Street NW, Suite 850, Washington, D.C. 20005 T 202 682 4292
Compete.org



Compete.

Council on
Competitiveness