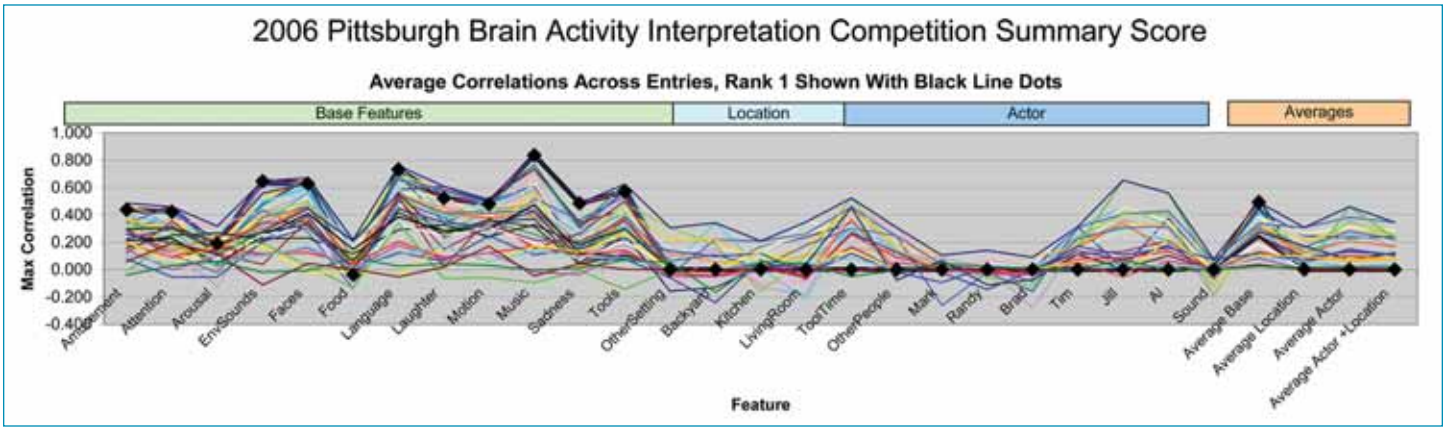
NewsBytes

Neurocomputation of Music, Faces and Belly Laughs

Peek inside the skull of a couch potato watching reruns on TV and you'll see non-stop patterns of blood flow throughout the brain. If you learn to pick out which activity patterns match up with, say, a good belly laugh, then you might be on your way to reading the viewer's internal experiences. Recently, experts from a variety of fields competed to glean subjective perceptions like humor from functional MRIs of TV viewers. They were surprisingly successful.

"Our goal is to know how the brain represents information," says **Walter Schneider, PhD**, professor of psychology at the University of Pittsburgh and principal investigator of the Experience Based Cognition group, which sponsored the competition. "In theory, if we can understand the information in the activity of somebody's brain, then we can understand what they perceived."

In the competition, 40 teams of researchers from nine countries developed pattern-classification methods for interpreting fMRI data. They used training data derived from three volunteers watching scenes from two episodes of "Home Improvement" 14 times each—



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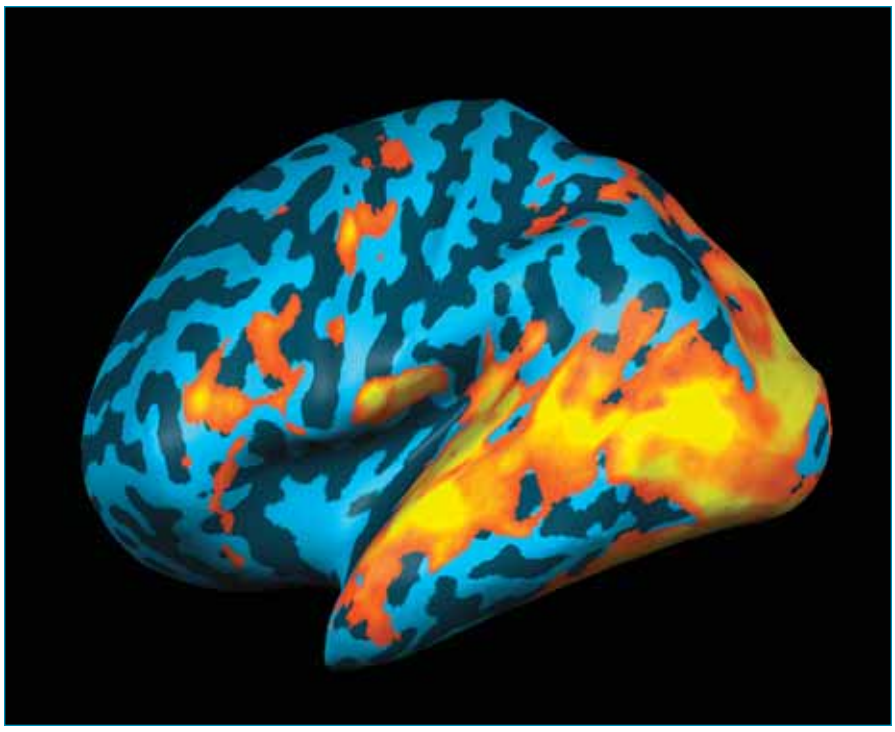


Above: Using brain activity patterns like those shown here (derived from fMRI), the winning team (Veeramachaneni's group) had the highest weighted average correlation for the prediction of various features of the volunteers' subjective viewing experience. Top: On the graph, the correlations of the team's predictions are shown in bold black; other teams' scores are shown in color.

once in an MRI scanner and 13 times while reporting their perceptions. The teams tested their methods on fMRI images of the volunteers watching a third set of scenes from the TV show. The goal was to decipher each individual's brain activation patterns and then describe his or her TV-watching experience in a way that would closely match the volunteer's real-time impressions. Winners were announced in June at the Organization for Human Brain Mapping meeting in Florence, Italy.

Overall, predictions were remarkably accurate, Schneider says. The easiest patterns to pick out in the fMRI data were those that occurred when volunteers heard background music. The top group's prediction for music perception was "almost right on top" of the volunteers' own ratings, he says, with an average correlation of 0.84. Patterns for faces, language, and environmental sounds were also generally easy to detect, and some groups excelled at identifying when the volunteers recognized specific actors in the scenes. On the other hand, nearly all groups stumbled at figuring out when food was visible on the screen. Perhaps the mere sight of food doesn't evoke strong signals in the brain, Schneider says, "although one subject did skip lunch, and we got better responses for him."

The top group, led by **Sriharsha Veeramachaneni, PhD**, a researcher at the Center for Scientific and Technological Research at the Istituto Trentino Di Cultura in Italy (ITC-IRST) with a background in computer engineering, built a model with recurrent neural networks. Despite knowing "practically nothing" about analyzing brain images, Veeramachaneni says, the researchers soon realized they could treat these signals as generic data for purposes of this competition.

The second-place team, led by **Denis Chigirev**, a physics doctoral student at Princeton University, concentrated on extensive preprocessing of the data across space and time—an approach that reflects the group's perspective. "Physicists pay careful attention to what is signal and what is noise," Chigirev says. "We wanted to let the signal tell us what to do."

Alexis Battle, a computer science doctoral student at Stanford University, led the third group which explicitly modeled correlations in the dataset. "We thought about the relationships in the data that we could exploit," Battle says. "We chose to encode the relationships in a formal probabilistic framework."

Schneider is already "playing matchmaker" to help facilitate new multidisciplinary collaborations next year. According to **Daphne Koller, PhD**, professor of computer science at Stanford University and principal investigator for Battle's team, "The fMRI field is at the point that genomics was 10 years ago. There's a tremendous opportunity now for us to integrate computational methods with the understanding that's being developed by the brain scientists."

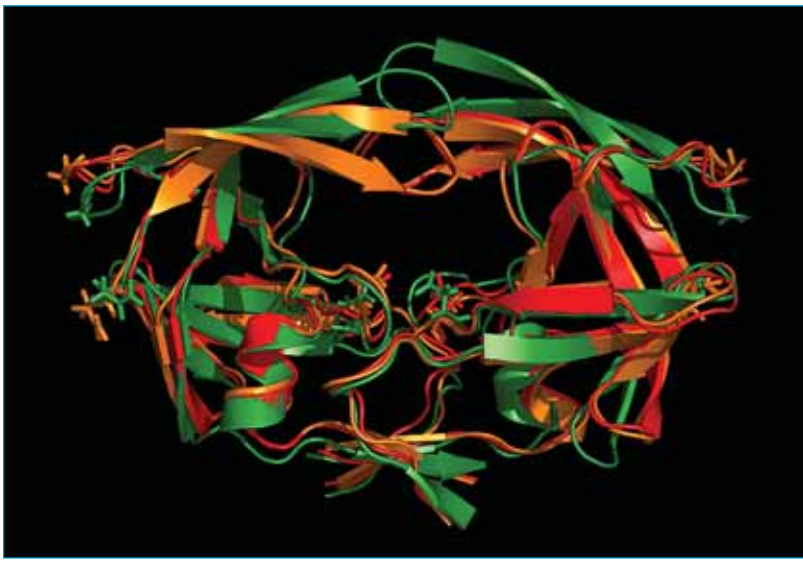
—Regina Nuzzo, PhD

Simulations Find Possible HIV Achilles' Heel

A blindside attack on HIV-1 protease might just combat drug-resistant strains of HIV, according to simulations run by researchers at the University of California, San Diego. When the simulations shut down an exposed movement on the side of the enzyme, the active site shut down as well. The work was published in *Biopolymers* in June 2006.

HIV-1 protease is an indispensable workhorse of the HIV virus: It cuts viral protein chains into building blocks ready for assembly into new virus particles. Many of today's anti-HIV drugs target this enzyme, generally by plugging up its active site and permanently closing two flaps over that area. In HIV strains resistant to these drugs, HIV-1 protease developed flaps

Perryman and his colleagues suggest designing drugs to target flap movement on HIV-1 protease instead of (or in addition to) the protein's active site.



A new target for anti-HIV drugs may be the allosteric grooves on the side of HIV-1 protease (see gaps in the middle of the right and left sides). When those are pinched together (see green protein, right and left sides), the flaps over the active site (top) can open. The flaps remain closed when the groove is propped open (red and orange versions). Courtesy of Alexander Perryman.

that are harder to latch shut. So now some researchers are suggesting targeting flap movement instead of (or in addition to) the active site.

That's why Alexander Perryman, PhD, now a postdoctoral fellow at California Institute of Technology, Andrew McCammon, PhD, professor of theoretical chemistry and pharmacology at UCSD, and their coworkers were very curious when they noticed an interesting movement on a side surface of HIV-1 protease in molecular dynamics simulations performed in 2004. When the protease closed its flaps across the active site, a groove on the peripheral surface expanded. Conversely, as the active site flaps opened, that same groove, called the allosteric groove, shrunk. It looked as if the movements were directly linked.

So the researchers hypothesized that inhibiting the movement of the allosteric groove would inhibit the movement of the active site flaps as well. In simulations that invoked an imaginary force or drug acting on the allosteric groove, they found their hypothesis was correct. When the allosteric groove is propped open by an imaginary drug, the flaps that guard the active site stay closed. And when the groove is pinched together slightly, these flaps will open.

It is still entirely unknown whether an actual drug exists, or could be created, that would apply the same force as the imaginary drug in the UCSD simulations. Celia Schiffer, PhD, associate professor of biochemistry and molecular pharmacology at the University of Massachusetts Medical School, thinks the groove movements are important for protease function, yet she is not convinced that the allosteric groove is a viable drug target. "I think practically that would be a very difficult place for inhibitors to bind in a specific and high-affinity manner."

But Carlos Simmerling, PhD, associate professor of chemistry at State University of New York, Stony Brook, is impressed by the UCSD strategy of finding a new drug target by observing enzyme movement. "The idea of targeting the mechanism is a lot more powerful than targeting the shape of the binding pocket, which is what current drugs do," he says.

—Louisa Dalton

Lung Tumors Recap Developmental Patterns

Researchers have long speculated that many of the genetic programs responsible for rapid growth of tumors are also important for the growth that occurs during normal embryonic development.

Now, researchers at the Children's Hospital Informatics Program at Harvard have found not only a relationship between tumors and lung development, but also a trend: The tumors with genetic profiles that resemble early lung development are deadlier than those with profiles that resemble later lung development. Separating out the least aggressive tumors from the more dangerous ones might help some lung cancer patients avoid unnecessary toxic chemotherapy. The work was published in *PLoS Medicine* in July 2006.

"Until now, lung cancers were classified through clustering of gene expression data, without seeing the trend from the point of view of development," says Hongye Liu, PhD, research fellow in the Children's Hospital Informatics Program at Harvard and MIT. "But we've found that the development trend can predict which cancer is worse."

Earlier work by Liu's co-authors, Alvin Kho, PhD, and Isaac Kohane, MD, PhD, showed that the gene expression profiles for each of several different types of brain tumors form distinct clusters when projected onto the gene expression profile of mouse genomic cerebellar development. The work by Liu and colleagues confirms these findings in the lung cancer context and takes them one step further by finding a connection between tumors, development and prognosis.

Charles Powell, MD, professor of clinical medicine at Columbia University College of Physicians and Surgeons, says Liu's work is important in emphasizing the link between cancer and development, but prognostic indicators in this paper need to be tested prospectively. More interesting, he says, is the potential

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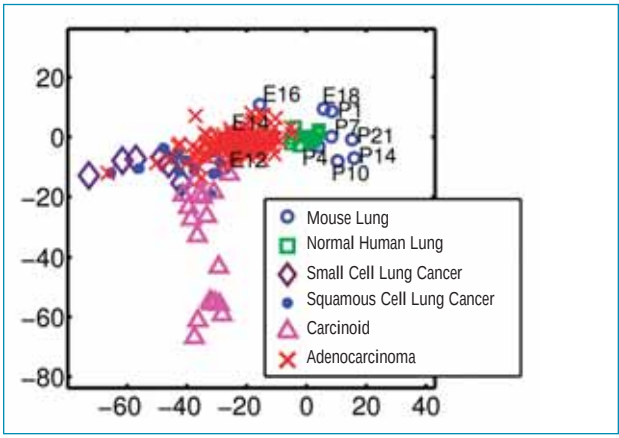


Principal components of gene expression data for mouse lung and normal human lung compared to that of various types of human lung cancer. The mouse lung development profile (blue dots) marches to the right over time. The most malignant forms of lung cancer (small cell lung cancer) more closely resemble early lung development in the mouse, while the least malignant forms (adenocarcinomas) more closely resemble later lung development in the mouse and normal human lung tissue. Carcinoids (purple triangles) are known to be quite different from the other types of cancers and have a pattern of gene expression that clusters perpendicular to and below the others. Carcinoids can look like small cell lung cancer under a microscope, but the two types of cancer require different treatments. This gene expression tool might help to distinguish them.

for insight into the origins of lung cancer. "The steps that transform a damaged cell into lung cancer of one type or another are likely to be similar to normal development in the lung," he says. "If we can follow-up this paper to understand those steps then we should be able to discover novel insights into lung carcinogenesis."
—Kathy Miller

Chain "A" of the protein Ubiquitin Hydrolase, which contains the most complicated knot that Grosberg and Lua found in a protein. It has a knot with at least five crossings in it when viewed as a flat object. Courtesy of Rhonald Lua.

Proteins in Knots? NOT!

When you accidentally twist a shoelace, garden hose, or necklace, it can get annoyingly tangled into intractable knots. On the microscopic level, biopolymers—string-like molecules such as DNA—also form knots, with one mysterious exception: knotted proteins are rare. Physicists have now used computational methods to quantify just how rare in the May 2006 issue of *PLoS Computational Biology*.

"We found that the proportion of proteins with knots is several orders of magnitude smaller than chance would predict," says author **Alexander Grosberg, PhD**, professor of physics at the University of Minnesota. "The degree of it is spectacular."

To envision a knot in a protein, imagine grasping the ends of an amino acid chain (the N-terminus and C-terminus), one end in each hand, and then stretching it out. If you can't stretch it into a straight line, then it contains a knot.

> "We found that the proportion of proteins with knots is several orders of magnitude smaller than chance would predict," says Alexander Grosberg.

Of course, finding knots in real proteins requires a computer rather than a pair of hands. Grosberg and his co-author, postdoc **Rhonald Lua, PhD**, developed a knot-detecting algorithm that they used to scan 4716 proteins with known shapes from the Protein Data Bank. They found only 19 proteins (0.4 percent) with knots. Bolstering their findings, two other groups (from MIT and Italy) independently arrived at almost the same list of knotted proteins (they missed two of Grosberg's).

Grosberg and Lua next set out to quantify how often proteins would be expected to form knots if only chance was at work. They simulated the shapes of random polymers with chains of equal length, density, and flexibility as proteins using a statistical technique—random walk on a lattice. Starting at a single point, this algorithm draws a path in three dimensions by randomly moving one unit at a time in one of six possible directions: up, down, forward, backward, right, or left. The end result is a randomly crinkled chain that may or may not contain knots. The proportion of these random polymers with knots trounced that found in real proteins: Simulated polymers at lengths of a typical protein (200-500 amino acids) formed knots 15-60 percent of the time.

Marc Mansfield, PhD, a professor of chemistry and chemical biology at the Stevens Institute of Technology, did pioneering work on knotted proteins in the early 1990s. He says the researchers' method of generating random polymers produces some bias, but the bias did not significantly affect the result and had no impact on the study's overall conclusions.

As to the mystery of why proteins avoid knots, Grosberg says "it has to be a product of evolution." Mansfield agrees: "My money is still on the explanation that a knotted protein just would not fold well, so nature doesn't use them."
—Kristin Cobb, PhD

Simulating Wheelchair Posture

Implanting electrodes into paralyzed torso muscles can help individuals with spinal cord injury balance in their seats. So say researchers at Case Western Reserve University, who have built a three-dimensional biomechanical model that predicts how effectively functional electrical stimulation (FES) stabilizes seated postures.

In 2003, the late actor Christopher Reeve received implanted electrodes for FES to help him breathe, and various other

For those with spinal cord injury, hooking one arm over an armrest for stability is a common strategy to maintain balance when reaching. Courtesy of Cleveland FES Center.

types of FES are under investigation for help in bowel and bladder control, coughing, walking, and standing. However, relatively little attention has been paid the subtle muscle movements of torso stabilization required for balanced, steady sitting, says Ari Wilkenfeld, MD, PhD, first author of the study that appeared in the March/April issue of the *Journal of Rehabilitation Research & Development*.

A stable seated position means being able to reach with one or both hands and not fall over, Wilkenfeld says. A healthy posture also prevents skeletal deformities, pressure wounds, and too much pressure on internal organs.

The Cleveland group's model of the human torso simulates how three muscle groups work in synergy to rotate the spine and bend it forward and sideways. Knowing from previous research that a paralyzed muscle stimulated by FES produces, at most, about 50 percent of the force of a non-paralyzed muscle, Wilkenfeld, along with investigators Ronald Triolo, PhD, and Musa Audu, PhD, at the Cleveland FES Center, used the model to calculate the largest range of stable movement that a paralyzed torso could attain under ideal FES.

They found that with the help of FES, paralyzed individuals can hold the weight of one or two bricks at arm's length, bend forward enough to extend their reach by almost a foot, and bend to the side a bit more.

In addition to creating the model, the Cleveland researchers compared its predictions to the actual sitting of a test volunteer with one pair of implanted spine electrodes. They found that one pair is not ideal because it does not fully activate even one of the sets of muscles. Yet they found that the model describes seated postures well.

"It is a promising start," says Jason Gillette, PhD, an assistant professor who specializes in biomechanics and motor control at Iowa State University. He suggests testing more individuals and expanding the tests to include active reaching, not just still postures.

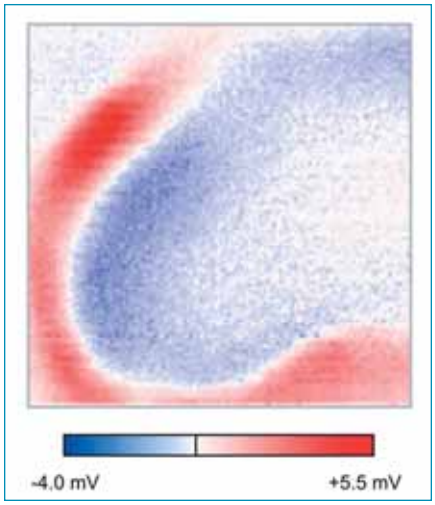
Additionally, says Wilkenfeld, they'll need a more sophisticated system of FES implanted electrodes to get the kind of results predicted by the model. Yet, now that they have a model that shows two-handed reach and the stable sitting postures theoretically possible, they can work on the practical details for attaining them.
—Louisa Dalton

Brain Chips

Neurons are tough cells to study. There are a staggering number of them in most animals, and they are constantly talking with one another. One way to look at groups of neurons in real-time is to take a slice of brain, stimulate it electrically, and measure responses across the slice. Now a new tool may give researchers more neuronal data in the span of a few milliseconds than ever before.

A team headed by Peter Fromherz, PhD, a director at Max Planck Institute for Biochemistry in Munich, has developed a computer chip that can measure the activity of thousands of neurons at a time. "We can get a movie of a complete electroactivity map in space and time, with a resolution of eight micrometers," Fromherz says. The work was published in the September 2006 issue of the *Journal of Neurophysiology*.

Fromherz's group worked with Infineon Technologies in Munich to create a special 1-square-millimeter silicon chip containing more than 16,000 transistors. To prepare the device for data collection, the researchers first culture a thin slice of rat hippocampus onto the chip for a few days. Then they stimulate the slice with microelectrodes and take an electrical snapshot every half-millisecond. "Transistors in the chip measure the voltages that arise in the slice, so we can see how electrical activity propagates in the tissue," Fromherz says.



Although the chips themselves are relatively simple, Fromherz says, the computer technology behind it is rather complicated. His team is retooling the apparatus so that it can run off a PC rather than the specialized computers used now. After that, they'll work to make the entire system commercially available for other scientists.

Fromherz's long-term goal is neurocomputing, a coupling of both brain and silicon. He hopes that semiconductor technology can eventually benefit from the brain's powerful ability to store memories. "Right now, that is a little bit science fictiony, I know," Fromherz says. But Fromherz has less lofty goals for the near future. He'd like to see the brain chip help pharmaceutical researchers expand their study of drug effects on the brain by providing data on thousands of neurons at a time. And he hopes that the technology will prove useful to neuroscientists who are open to new technology. "Now the neuroscientists have a new tool, and they will need to think about completely new questions," Fromzherz says.

Indeed, it remains to be seen how useful this chip will turn out to be for brain researchers, says Arthur Toga, PhD, professor of neurology at the University of California, Los Angeles. "But I'm a firm believer that almost every leap forward in neuroscience has been preceded by a technological innovation, one that allows us to pose questions that couldn't be posed before," he says. "That's been true all the way from the microscope to the MRI."
—Regina Nuzzo, PhD □

Fromherz and his colleagues used more than 16,000 transistors on a 1-square-millimeter silicon chip to measure field potentials from a slice of rat brain every half-millisecond after stimulation with electrodes. This image shows those potentials after 5 milliseconds have elapsed. Red regions indicate positive voltage; negative signals are in blue. The gray curve traces the structure of the cornu ammonis in the hippocampus.