

# IMAGING UPDATE

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## YALE UNVEILS NEGATIVE-STIFFNESS VIBRATION ISOLATION IMAGING

Led by Professor Lawrence E. Cohen Ph.D. of Yale University's Department of Cellular and Molecular Physiology, the small lab in room BE58 at the Yale School of Medicine has been conducting research on neuronal activity in brain cells to develop methods for imaging brain activity, and then uses these methods to study the brain. The university has been developing the method for imaging brain activity for 42 years, but it was not until several years ago that the lab opted to move to a higher level of vibration isolation technology to support its microscopy imaging which it conducts at the micron level.

It is not unusual for universities, and industry for that matter, to have to deal with problems in site vibration which compromise to a greater or lesser degree the imaging quality and data sets which they acquire through microscopy. Although it is certainly the desire of every lab to rid the unwanted vibration, conventional systems such as air tables which many universities and industry labs still use, have not been successful in providing an adequate level of vibration isolation for ultra-sensitive equipment measuring at the Angstrom and micron levels.

Such was the case with Dr. Cohen's lab at Yale, where air tables had been the mainstay for the lab's vibration isolation for many, many years. But now, for adequate isolation to conduct its neuronal research at the micron level, the air tables were not able to provide the vibration isolation needed for the lab's research.

### Measuring Brain Activity

"One reason the brain is difficult to study is that many individual neurons or brain areas are active at once, and conventional electrode techniques allow monitoring of only one or a few neurons or locations at a time," said Dr. Cohen. "We have worked on several variations of an optical method for measuring brain activity, utilizing both voltage-sensitive and calcium-sensitive dye methods to study neuron activity, and in favorable preparations the spike activity

of about 500 individual neurons or thousands of brain regions can be monitored simultaneously. These methods have good temporal (msec) and spatial (10s of microns) resolution."

"Monitoring many neurons or regions simultaneously can improve our understanding about how nervous systems are organized," continued Cohen. "Recently, we have used these methods to study the processing of olfactory information in the turtle and mouse. We have obtained maps of the input to the olfactory bulb which define the responsiveness of individual olfactory receptor proteins. In the future, we hope to obtain maps of the output of the bulb. A comparison of the two maps can provide a powerful description of the role of the olfactory bulb in processing olfactory signals."

"Basically, depending on the dye, we are viewing the voltage across the neuron membrane or the calcium concentration inside the neuron," Cohen adds. "When the action potential travels along the nerve and comes to the nerve terminal it releases a chemical that acts on the adjacent nerve cell. In order to release that chemical it opens a calcium channel. Calcium comes into the nerve terminal, and that calcium causes a vesicle - which is filled with chemical substances, to fuse with the membrane, and the transmitter substance is released."

"The voltage is the signal that the cell uses to carry information from one end to the next," explains Cohen. "For example, the cells in your spinal cord have to get information from your toe, and also send information to your toe. That signal is a propagated electrical wave of membrane potential, and dyeing that membrane can provide an optical signal that is used to measure that propagated wave."

#### Precision Equipment

The lab uses a high-speed camera to view these changes. It has a speed of 2,000 frames-per-second with very high quantum efficiency, which is the quantity of photons that get converted into electrons. The camera has a quantum efficiency of about .9, which converts almost all the photons into electrons. (In contrast, photographic film has a quantum efficiency of <.01, converting less than 1 percent of photons into darkened silver grains.)

In the lab's optical monitoring of brain activity, each pixel in the recording receives light from a small portion of neurons which have been stained by microinjection of the dye into the brain. After waiting for the dye to spread into the processes, the dye can be used to monitor changes in membrane potential in dendrites and axons.

When a low magnification objective is used to form an image of a vertebrate preparation on the lab's 464 element photodiode array or 80 x 80 pixel CCD camera, each pixel receives light from hundreds or thousands of neurons. The signals are the population average of the membrane potential or calcium concentration changes in those neurons. These population signals monitor coherent activity - those events that involve simultaneous changes in activity of a substantial fraction of the neurons in the imaged region.

It is also using a variety of microscopes to conduct this research including a laser scanning 2-photon microscope, and an optical microscope. At this time, only the optical microscope is set on the Negative-Stiffness vibration isolation system, built by Minus K Technology (<http://www.minusk.com>).

#### Vibration Noise

"Measuring in the dimension of microns still requires vibration isolation because it is so small," said Cohen. "Any small movement in the lab environment makes a big effect. If you are viewing at ten microns, and it vibrates by ten microns then you are in big trouble."

"We were using air tables before, but the Negative-Stiffness isolator is much better," Cohn continued. "It reduces the vibration by a larger fraction because it reduces the vibration in the X/Y plane just as well as in the Z plane, where the air table does not do well at all on the X/Y plane."

"For years we have worked hard to get rid of vibration noise, with only partial success," Cohen added. "Our lab is located one floor above the basement. Having been in the business a long time I know if we were in the basement it would be better. I have had my lab in places that are quieter. Since we put in the Negative-Stiffness system several years ago, we have not had to think about vibration noise at all. Before, there was always vibration noise, and

I would spend 5 to 10 percent of my time worrying about vibrations."

#### Negative-Stiffness Vibration Isolation

Negative-Stiffness isolators employ a unique - and completely mechanical - concept in low-frequency vibration isolation. Vertical-motion isolation is provided by a stiff spring that supports a weight load, combined with a Negative-Stiffness mechanism. The net vertical stiffness is made very low without affecting the static load-supporting capability of the spring. Beam-columns connected in series with the vertical-motion isolator provide horizontal-motion isolation. The horizontal stiffness of the beam-columns is reduced by the "beam-column" effect. (A beam-column behaves as a spring combined with a Negative-Stiffness mechanism.) The result is a compact passive isolator capable of very low vertical and horizontal natural frequencies and very high internal structural frequencies. The isolators (adjusted to 1/2 Hz) achieve 93% isolation efficiency at 2 Hz; 99% at 5 Hz; and 99.7% at 10 Hz.

#### Vibration Isolation in Bio-Research

Yale University has put into place a vibration isolation solution which correctly matches the precision level of the research the lab is undertaking. It is critical that researchers apply the correct vibration isolation solution to their sites. Putting up with lab vibration noise problems for any amount of time, let alone for a period of years, can only be costly in terms of lost production, and will certainly inhibit the progress of the research.

Bio-research is expanding at a huge rate into scores of different disciplines and literally hundreds of diverse applications. This will inevitably mean a sizable increase in the number of non-optimum, high-vibration-prone labs sites that will be in desperate need of truly functional vibration isolation. Hopefully, with the help of Negative-Stiffness vibration isolation, your site will not be one of them.

Dr. Lawrence B. Cohen is Professor of Cellular & Molecular Physiology at Yale University, School of Medicine, Department of Cellular & Molecular Physiology. He holds a B.A. from the University of Chicago, and received his Ph.D. from Columbia University in 1965. He can be reached at Yale

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Dr. David L. Platus is the inventor of negative-stiffness mechanism vibration isolation systems, and president and founder of Minus K Technology, Inc. (<http://www.minusk.com>). He earned a B.S. and a Ph.D. in Engineering from UCLA, and a diploma from the Oak Ridge School of (Nuclear) Reactor Technology. Prior to founding Minus K Technology he worked in the nuclear, aerospace and defense industries conducting and directing analysis and design projects in structural-mechanical systems. He became an independent consultant in 1988. Dr. Platus holds over 20 patents related to shock and vibration isolation.

Minus KR Technology, Inc. was founded in 1993 to develop, manufacture and market state-of-the-art vibration isolation products based on the company's patented negative-stiffness-mechanism technology. Minus K products, sold under the trade name Nano-KR, are used in a broad spectrum of applications including nanotechnology, biological sciences, semiconductors, materials research, zero-g simulation of spacecraft, and high-end audio. The company is an OEM supplier to leading manufactures of scanning probe microscopes, micro-hardness testers and other vibration-sensitive instruments and equipment. Minus K customers include private companies and more than 150 leading universities and government laboratories in 25 countries.

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#### ICX WINS 1.13 MILLION AWARD FOR U.S. ARMY INFRARED CAMERAS

ICx Technologies (NASDAQ:ICXT) , a developer of advanced technology solutions for homeland and military security, has announced that its ICx Imaging Systems unit has won a \$1.13 million award for delivery of DefendIR infrared cameras for use by the U.S. Army.

The Army will use the DefendIR units to support Military Operations on Urban Terrain (MOUT) training. The cameras use VisionSense(TM) technology, which blends the thermal image

with the visible image, enabling commanders to better observe and evaluate MOUT training exercises.

DefendIR is well-suited for MOUT training and evaluation," said Nirav Pandya, general manager of ICx Imaging Systems. "The setting on the camera can fuse, or overlay, the two images-thermal and visible-so users can get all necessary information in a single image."

The ICx DefendIR is an industry-leading, mid-range thermal imager that can see in complete darkness and through a multitude of environmental conditions including smoke, rain, snow, dust, and dense fog. Proprietary VisionSense technology combines video feeds from both a visible light (CCD) camera and the Defend IR, offering user-controlled customized mixing and merging of the two visual sources. This allows operators to penetrate glare and see through windows, glass, or water, which can be problematic for conventional thermal cameras.

#### About ICx Technologies(TM)

ICx develops advanced technologies for effective security solutions. ICx sensors detect and identify chemical, biological, radiological and explosive (CBRNE) materials. Icx surveillance products discern people and objects invisible to human senses and conventional cameras. ICx software and systems connect, command and control these security devices, while its intelligence and special-operations experts provide the unique insight that drives the company's innovation. Icx has manufacturing and research facilities in the United States, Canada and Europe.

For more information, visit <http://www.icxt.com> or call 202/298-7600, ext. 202.

#### CARL ZEISS MICROIMAGING UNVEILS AXIOVISION ASSAYBUILDER

Carl Zeiss MicroImaging, Inc. has unveiled a new technology that delivers high content analyses to research microscopes. The product ASSAYbuilder is a suite of next generation High Content Analyses (HCA) tools that can be added to any microscope with a digital imaging package including AxioVision. For the first time, any researcher can upgrade their ZEISS microscope to an HCA system at a fraction of the price of existing high content screening systems.

High content screening has accelerated drug discovery in the pharmaceutical industry for years. Leveraging the power of research microscopy for high content analyses promises to enable precise assay development and hit qualification for the screening community, while reducing the access cost for academics that need greater flexibility when imaging and analyzing biological targets. "We are excited about pairing High Content Analyses with high resolution imaging, confocal microscopy, and advanced digital imaging modalities," stated Martin L. Pietila, associate product manager for High Content Analysis at Carl Zeiss.

"Bridging research microscopy and screening constitutes a continuum of technology in the biomedical imaging market. By leveraging our experience with the Thermo Scientific Cellomics product line we have matched the best in class imaging with the best in class high content analysis technology," stated James A. Sharp, president and CEO of Carl Zeiss MicroImaging, Inc.

#### About Carl Zeiss

Carl Zeiss MicroImaging, Inc., a subsidiary of Carl Zeiss, Inc., offers microscopy solutions and systems for research, laboratories, routine and industrial applications. In addition, Carl Zeiss MicroImaging markets microscopy and digital pathology systems for the clinical market, as well as spectral sensors for industrial and pharmaceutical applications. Since 1846, Carl Zeiss has remained committed to enabling science and technology to go beyond what man can see. Today, Carl Zeiss is a global leader in the optical and opto-electronic industries.

With 11,249 current employees in the Group and offices in over 30 countries, Carl Zeiss is represented in more than 100 countries with production centers in Europe, North America, Central America and Asia. For more information, visit <http://www.zeiss.com/micro> or call 914/681-7627.

#### NOVADAQ'S SPY IMAGING SYSTEM NAMED "PRODUCT OF THE YEAR"

Novadaq(R) Technologies Inc. (TSX: NDQ), Toronto, a developer of real-time medical imaging systems and image guided therapies for the operating room, has announced that it is the recipient of the Frost & Sullivan North American Medical Imaging Product of the Year award for its SPY(R) Intra-operative Imaging System.

"I am so proud of the creative, and committed team at Novadaq whose efforts are reflected in this honor," said Novadaq president and CEO Arun Menawat. "Our mission is to greatly improve the lives of patients undergoing complex surgical procedures such as cardiac surgery, by enabling surgeons with clinically relevant intra-operative imaging."

SPY is the first and only fluorescent imaging system cleared by the U.S. Food and Drug Administration (FDA) that enables cardiac surgeons to visually assess bypass graft functionality during coronary artery bypass procedures. SPY is also ideal for use during technically demanding plastic and reconstructive surgical procedures such as breast reconstruction and other demanding free flap surgeries.

SPY combines a fluorescent imaging agent, a sophisticated laser light source and high-speed imaging to produce real-time images during the course of surgery in the operating room. The use of SPY has been shown in independent clinical studies reported in peer reviewed literature to reduce complications, improve patient outcomes and reduce the incidence of repeat cardiac procedures. The SPY technology is also cleared for use in plastic and reconstructive microsurgery, and is being evaluated for its potential in organ transplantation, pediatric surgical and urological procedures.

"Novadaq's introduction of SPY, a flexible and easy to use intra-operative imaging system, has the potential of revolutionizing the quality of surgical procedure in the operating room," said Frost & Sullivan Industry Analyst Samantha Barbosa. "For the first time, imaging can now be part of the continuum of therapeutic care before, during and after surgery for better patient outcomes."

Earlier this year, the United States Centers for Medicaid and Medicare issued a new procedure code for imaging procedures performed using the SPY System during cardiac surgery. This year's recognition of SPY is the second time Frost & Sullivan has acknowledged Novadaq's contribution to medical technology development. The global growth consulting company honored the SPY System in 2006 as its Cardiac Imaging Technology Innovation of the Year recipient.

For more information, visit <http://www.novadaq.com> and <http://www.awards.frost.com> or call 905/629-3822, ext. 202.