QB3 Brings the Science of Numbers to Biology

By Lisa Samols

Ask the average scientist to predict the future, and he or she may describe therapeutic cloning, artificial wombs or engineered plants. However, there are some who see something on a completely different scale. The California Institute for Quantitative Biomedical Research (QB3) has seen the future of biology, and it is made of numbers.

"We are currently living through a revolution in biomedical knowledge," says Marvin Cassman, Executive Director of QB3. "Biomedical research and the quantitative sciences—mathematics, physics, chemistry, and engineering—are teaming up to unravel the complexities of whole living systems."

Dr. Cassman joined QB3 in May 2002 after nine years as Director of the National Institute of General Medicine Sciences (NIGMS). The group that he leads consists of researchers from the departments of biological sciences, chemistry, mathematics, physics and computer sciences at the University of California Berkeley, UC San Francisco and UC Santa Cruz.

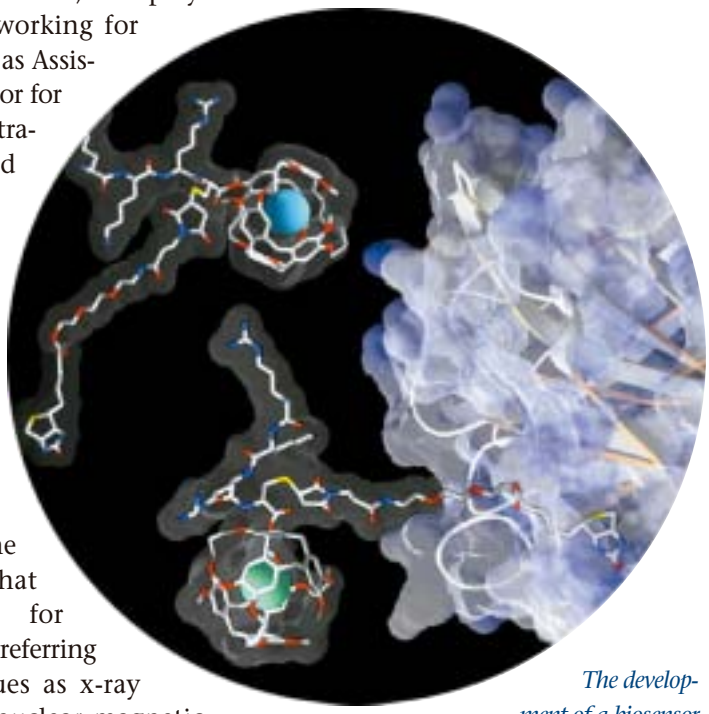
QB3 envisions biology as a multi-disciplinary science that uses the ideas behind chemistry, engineering, mathematics, and computer science to organize and enhance the utilization of biological information. Given the amount of information that has been accumulated so far in the history of modern biology and the rate at which new information is being gathered, the researchers at QB3 see a hard science approach as the only way to make sense of all of these ideas.

"In a day's experiment, you could accumulate more data than you could handle in weeks, and it takes computational science to organize it and make that data meaningful," says W. Sue Shafer, Deputy Director of QB3. Dr. Shafer was also at NIGMS, as Deputy Director, before working for UC San Francisco as Assistant Vice Chancellor for Research Administration. She joined QB3 in June 2002.

According to Dr. Cassman, the idea of blending the physical sciences with biology is not a completely novel idea. "We're implementing the kinds of things that have happened for decades," he says, referring to such techniques as x-ray crystallography, nuclear magnetic resonance and other types of spectroscopy, all well-developed fields of research that are based on the theories of chemistry and physics.

Using computer models to examine the interactions of proteins and algorithms to find patterns in the human genome, the researchers at QB3 intend to examine biological systems at all levels down to the component atoms and quarks. In cross-disciplinary, interdepartmental groups, they will investigate bioengineering and biotechnology; bioinformatics and computational biology; structural and chemical biology; and experimental genomics, proteomics and biochemistry.

QB3 is one of four interdisciplinary institutes created as the California Institutes for Science and Innovation (CISI) to stimulate the California economy through research. Despite the current budget crisis that threatens to drastically reduce funding for all academic institutions in California, Communications Manager Beth Martin at QB3 is confident that the institute will



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be set up as planned, and that it will have a positive effect on the state's economy in the long run.

UC Berkeley broke ground this May for the new Stanley Bioscience and Bioengineering Facility for QB3. At UC San Francisco, QB3 will soon be housed in a new building at Mission Bay, and the Physical Sciences building at UC Santa Cruz, part of which will house QB3 researchers, is currently under construction. The close proximity of the institutions is meant to encourage collaboration. For example, while the bioengineering and biotechnology group builds a microarray chip, the bioinformatics and computational biology group could work on identifying the gene, while the structural and chemical biology group would collect data on the gene's expression.

"The idea of three major universities coming together to pool their resources and tackle a wide class of fundamental problems in biomedical sciences is extraordinarily exciting," according to David Agard, UC San Francisco QB3 Director.

In addition to such collaboration, QB3 will make available its facilities and work with California industry on basic science projects. By buying into a consortium or paying a fee per use, companies can gain access to QB3's light microscopy facility, microarray service and protein expression facility, among many others.

"We have the ability to move quantitative bioscience into the mainstream, train a new generation of researchers, and bolster the California economy through job creation and product development," said Dr. Cassman.

Artificial Sight

Dr. Wentai Liu, Professor of Electrical and Computer Engineering at UC Santa Cruz, is developing a way to help the blind see again. By replacing photoreceptors in the retina with a device that sends electronic impulses to the neurons of the eye, Dr. Liu and his team hope to imitate what happens in a normal eye.

"The point of the research is to try to understand the visual process and come up with a device to help the brain restore vision," said Dr. Liu.

In retinitis pigmentosa and age-related macular degeneration, the leading causes of blindness, photoreceptors die off, but the neurons to which they are connected frequently survive. Photoreceptors detect light from the outside world and stimulate neurons, which send the message to the brain to be translated into an image. When the photoreceptors are damaged, no visual information gets to the brain.

When Dr. Liu and his team found that visual sensation can be elicited by electrically stimulating the neurons just as the information from the photoreceptors did, the next task was to develop a device that could stimulate a number of neurons individually, as if they were several separate photoreceptors.

"In the beginning, it sounded like science fiction," he recalled. As the idea progressed, however, his team found that restoration of sight using electronic impulses was an attainable goal.

The result of years of engineering research is a 4.5 mm by 4.5 mm chip that picks up signals sent by a camera embedded in a pair of glasses that the patient wears. The camera translates light into electronic information, which it transmits to the chip in the eye. The chip can then stimulate the appropriate neurons with 64 electrodes, simulating the actions of the photoreceptors.

Dr. Wentai Liu of UC Santa Cruz, is developing a way to help the blind see again.

Initial clinical trials of the first generation of the retinal implant have yielded promising results. Three patients received permanent implants at Doheney Retina Institute, University of Southern California, and all three can sense motion, recognize objects and read large letters, though only in gray level.

Using Biomemetics Microelectronic Systems, a program involving labs from University of Southern California, UC Santa Cruz, and the California Institute of Technology, Dr. Liu hopes to design a chip with 1000 electrodes that would allow formerly blind patients to read and recognize faces.

Diagnostic Chemistry

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ASBMB member David Wemmer and Alexander Pines, both Professors of Chemistry at UC Berkeley, have combined their fields of research to develop a sensitive biosensor that can determine the amount and location of certain target biological substances. Dr. Peter Schultz at Scripps Research Institute is playing a key role in implementing the ideas.

The biosensor is built on the concept that hyperpolarized xenon atoms give particularly bright NMR spectra that

change significantly when they interact with other substances. Dr. Pines' lab had been working with xenon to probe various materials, using the hyperpolarized version to generate the brightest NMR spectrum. Dr. Wemmer's lab then helped find a way to make the sensitive hyperpolarized xenon interact with biological substances.

"This is going from atomic physics to do the hyperpolarization, to biology to use it, while going through chemistry in the middle," said Dr. Wemmer.

To make the xenon, a noble gas, interact with biological substances, a cryptophane was used to provide an artificial pocket for the xenon. The cryptophane, a 'cage' comprised of six benzene rings, was tethered to a ligand, which can bind to a specific

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target substance. When the ligand portion is bound to a particle such as a protein, a different NMR spectrum is read for the xenon which is being carried along. So far, a version of the biosensor has been chemically synthesized in Dr. Schultz's lab that uses a biotin ligand to bind to avidin, but in theory, anything from antibodies to ligands for proteins on cell surfaces can be used to detect the presence of cancerous cells or foreign bacteria or viruses in the human body.

According to Dr. Wemmer, the biosensor relies on the ligand binding specificity to differentiate between similar substances. He believes that different versions can be made which can be read out in parallel to detect different compounds, although many practical issues remain to be worked out. At present, biosensors have been used only to determine the relative amount of the substance present, and its location in the solution. However, Dr. Wemmer's research may eventually lead to new, non-invasive techniques for detecting disease.