Deedee Meldrum and the "Life-on-a-Chip" Center

by Marita Graube

Just as Henry Ford's assembly line churned out an unprecedented number of Model Ts, automated instruments for the Human Genome Project have revolutionized the DNA sequencing process. One of the scientists leading this "Industrial Revolution" for biology is University of Washington professor Deirdre Meldrum.

Deirdre Meldrum. Photo: Kathy Sauber/ UW Photography

As director of the UW Genomation Lab, Meldrum helped automate and miniaturize sample-handling techniques for DNA sequencing in the Human Genome Project. Her work was honored when the National Institutes of Health (NIH) created a Center of Excellence in Genomic Science, naming Meldrum as the principal investigator.

The center is made up of several local labs, including Meldrum's Genomation Lab. The creation of the center came with a $15-million grant through the National Human Genome Research Institute of the NIH.

Collaborating with a multidisciplinary team, Meldrum is trying to create the technology that will enable scientists to understand how individual cells and genes function. Their ultimate goals are to achieve rapid diagnoses, design individually-tailored treatments, and develop new ways to prevent disease.

Meldrum, called Deedee by her coworkers, knows that her position is unique. The NIH named only three academic Centers of Excellence in Genomic Science (CEGS). The second center is at the UW's School of Medicine Genome Center directed by Maynard Olson. Yale University houses the third.

With co-director Mary Lidstrom, associate dean of the UW College of Engineering, Meldrum has formally named their operation the Microscale Life Sciences Center, but its nickname is "Life-on-a-Chip," because they want to keep cells alive on a chip and analyze multiple parameters of the cell in real-time.

"The goal is to detect and analyze how, when, and why very small populations of living cells interact with each other and their environment," says Meldrum. "This will allow scientists to relate specific genes to specific cellular processes."

Although Meldrum is excited about the Life-on-a-Chip center, she wasn't initially involved in genetic research. An early passion for math and architecture led to an engineering education, focusing on robotics, dynamics, and control. However, while finishing a doctorate in electrical engineering at Stanford, she had a friend who read a lot about genetics and saw a need for Meldrum's talents. "He said to me, 'Deedee, they really need automation in the Human Genome Project.'"

Soon after hearing this advice, Meldrum arrived at the UW electrical engineering department at the same time as the UW department of molecular biotechnology was starting up. She became involved in the biotechnology department meetings, and in 1993 she received an NIH training grant to study genetics and biology. "I was in the right place at the right time," laughs Meldrum. "Things just started falling into place."

Meldrum applied her knowledge of control systems and automation to assist biologists with sample preparation, handling, and analysis.

It was 1994, and processing samples for the Human Genome Project was costly and slow. To address the need for automated systems with smaller sample volumes, Meldrum established the Genomation Lab. There, she helped develop an instrument called Acapella-1K.

Using glass capillaries to obtain DNA samples, Acapella-1K processed 1,000 samples in eight hours. The system was automated to perform the reactions required in the genome sequencing process. It was over ten times faster than the manual process employed up to that time.

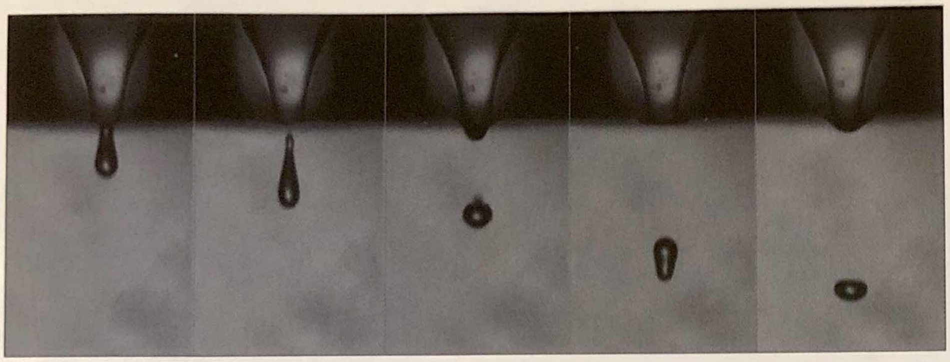
Meldrum observes the Acapella-5K as it rotates through samples. This system has automated and increased the speed of sample handling for DNA sequencing by 10 to 100 times. Photo: Kathy Sauber/UW Photography

Acapella-1K marked Meldrum's first step towards making an automated system designed to reduce the time and cost of mixing reagents. Now, working with Orca Photonic Systems, Inc. of Redmond, Wash., she is developing Acapella-5K, which processes 5,000 samples in eight hours.

Slightly larger than a microwave oven, Acapella-5K resembles a space-age kitchen widget. Although it doesn't slice, dice, or whip, it can mix and measure fluid samples as small as 500 nanoliters (or 20 times smaller than a drop of water). A central carousel holds numerous glass capillaries, ex-

"Life-on-a-Chip" Researchers

Project	Investigators
Metabolism	Mary Lidstrom UW ChemE/Microbiology
Infection	James Mullins John Mittler Brad Cookson UW Microbiology
Rare Proteins	Norman Dovichi UW Chemistry
Cancer Biology	Brian Reid Fred Hutchinson Cancer Research Center
Microfabrication	Karl Böhringer UW Electrical Engineering
Sensor Fusion	Denise Wilson UW Electrical Engineering
Detection	Lloyd Burgess Brian Marquardt UW Chemistry
Nanotechnology	Viola Vogel UW Bioengineering
Systems Integration and Control	Deirdre Meldrum Mark Holl UW Electrical Engineering



A 100 picoliter droplet, about 100,000 times smaller than a drop of water, squeezes out of an Engineering Arts piezoelectric dispenser.

tending horizontally from the center. Each capillary is about the length of a toothpick but is only 340 microns in diameter, about the width of five human hairs.

Every five seconds, the capillaries rotate like slides in a projector, as the Acapella-5K cycles through each sample, making a "whoosh." With each pass, the machine is turning the capillaries to one of eighteen stations, where it adds or mixes the fluid samples.

At some stations, a dispenser squeezes tiny drops into the capillary tube. Meldrum explains that the drops shoot across the air. No contact is made between the dispensing station and the capillary in order to avoid cross-contamination.

"The Acapella-5K capillary system," says Meldrum, "has automated and sped up liquid handling for sequencing by ten to one hundred times." It has decreased the costs by about a factor of ten, and increased reliability and repeatability for the samples prepared, she says.

The success of the Acapella system has been widely recognized. In 1996, she earned a Presidential Early Career Award for Scientists and Engineers, which was awarded by then President Clinton.

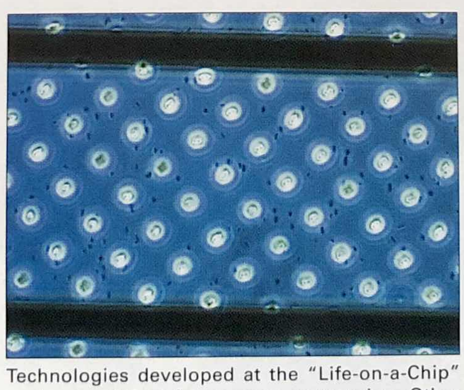
With this award, Meldrum began to work on developing microsystems in the Genomation Laboratory. Microsystems are tiny devices on the scale of micrometers with features such as micro-scale detectors, tiny motors, and micro-sized liquid handling capabilities.

With the UW's Mark Holl, she started laying the groundwork for what became the Microscale Life Sciences Center.

Meanwhile, with a separate grant through the NIH National Cancer Institute (NCI), Meldrum's team started developing other prototypes. One device performs the polymerase chain reaction (PCR), the reaction used, for example, in DNA fingerprinting to copy DNA.

The PCR process is used to amplify a DNA sequence so that there is enough DNA to be adequately tested. First, the DNA is heated to split its double-helix structure into two separate strands. Substances that contain the individual building blocks of the DNA are added to the solution. The solution is then recooled and the strands attach to their specific building blocks, recopying and extending the DNA sequence. After running this process 30 times, the DNA is amplified over a millionfold and ready to be tested.

In a typical run of PCR, a researcher repeats the process up to 30 times before analyzing a DNA strand. With real-time quantitative PCR, the researcher can monitor the process as it happens to look for disease or deletion in the DNA strand, without waiting for all of the cycles to run. The technology involves shining a laser onto the sample and measuring the fluorescent intensity that results.



Technologies developed at the "Life-on-a-Chip" center aren't just for genome sequencing. Other applications include separations technology like dielectrophoresis—a kind of "obstacle course" used here to separate bacteria by age and size. When placed in a fluid under an alternating electric field, smaller bacteria will move faster through the course than larger ones. In this image, electrodes are the lines across the top and the bottom. The white circles are the posts that create obstacles for the bacteria (tiny dark spots) to go around. Photo: Kosar, Holl, Meldrum

This real-time process will be used in the NCI project to detect disease. "For example," explains Meldrum, "if someone had been treated for leukemia and you took a blood sample to see if there was just one cancer cell remaining in their system, we could ideally detect that one single cell."

Eventually, real-time quantitative PCR will be built into a module that also works with the Acapella system.

The center's instruments aren't just for genome sequencing. Other applications include separations technology—for instance, a kind of "obstacle course" used to separate bacteria by age and size. When placed in a fluid, the bacteria respond to alternating electric fields such that the smaller bacteria (the younger ones) will move faster through the course than the larger (older) bacteria. Once the bacteria are separated by age, the researchers can conduct further studies.

"These microsystems were precursors to the new center of excellence," says Meldrum. The Life-on-a-Chip center will continue to develop the microsystems as it works with groups across campus and with researchers at the Fred Hutchinson Cancer Research Center.

Results of the research will become part of modular microsystems, or "tool kits" for bench researchers. The tool kits will have different modular devices that a researcher can put together to run experiments. "The idea is to enable the researchers to have the flexibility to keep changing the system," explains Meldrum.

In the next few years, Meldrum's team plans to build two more Acapella systems, increasing the number to four. The systems will be tested in three large genome centers: The UW Genome Center, the Washington University Genome Sequencing Center in St. Louis, and the Whitehead Institute/MIT Center for Genome Research in Cambridge, Mass. There will be only four Acapella systems in the world. Meldrum smiles, "We're one of a kind right now." ■

Marita Graube recently received a bachelor's degree in technical communication from the University of Washington.