解説

Automated Systems for Genome Analyses

—Technologies Enabling Advances in Science to Improve Human Health—

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1. Genomation Laboratory

In 1993, I founded the Genomation Laboratory at the University of Washington (UW) to develop automated, high-throughput, integrated instruments to process nanoliters to microliters of fluid for biochemical analyses. With initial support from the Washington Technology Center and strong support from the National Institute of Health (NIH) National Human Genome Research Institute, we have developed a capillary-based instrument, ACAPELLA (**Fig. 1**), to process 5,000 samples in 8 hours for polymerase chain reaction (PCR), quantitative PCR (qPCR) for minimal residual disease [1], deoxyribonucleic acid (DNA) sequencing reactions, protein crystallography, and the potential for application in drug discovery, forensics, and DNA analysis of environmental samples. The system takes DNA or other chemical samples and automatically processes them as specified in a user-defined protocol with sample aspiration, reagent dispensing, mixing, thermal cycling, and intermediate imaging steps. A serial pipeline process is used to provide flexibility, reproducibility, and reliability of the reactions prepared. For genome analyses applications, ACAPELLA has been optimized for sample volumes in the range of 0.5~2 [L].

Other projects in the Genomation Laboratory include the development of a new system for automated protein crystallization, screening, and optimization from incoming purified proteins to outgoing crystal samples ready for crystallographic analysis. This system requires robotic handling of capillaries and automated imaging to detect and classify protein crystals.

Fig. 1 ACAPELLA automated biochemistry system

Additionally, we are developing a system to automate cell preparation in tubes for 3D microscopy. We are creating an automated sample preparation instrument and associated reagents/methods for the debulking and cleanup, enrichment, and staining of cells-of-interest in support of automated high-throughput 3D microscopy for analysis including cancer detection and diagnosis. Specimen types of specific relevance to this development effort include lung sputum, gynecological specimens, colorectal specimens, fine needle aspirates, urinary tract, and gastrointestinal specimens.

2. Microscale Life Sciences Center

In 2001, the Genomation Laboratory teamed with other investigators to form the Microscale Life Sciences Center (MLSC), a National Institutes of Health (NIH) National Human Genome Research Institute (NHGRI) Center of Excellence in Genomic Science (CEGS). The MLSC or “life-on-a-chip” (<http://www.life-on-a-chip.org>), directed by D. Meldrum and M. Lidstrom, is one of the first of nine CEGS funded by the NIH NHGRI. It involves ten investigators from the UW Departments of Electrical Engineering, Chemical Engineering, Materials Science and Engineering, Chemistry, Microbiology, Laboratory Medicine, and the Fred Hutchinson Cancer Research Center. The Center is funded for 5 years at \$15 million, and will be renewed

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for another 5 years through 2011.

The MLSC is developing microscale instrument modules to measure multiple parameters in living cells in real time to correlate cellular events with genomic information (e.g. gene expression and genomic rearrangements) [2]. These modules comprise a low-cost, flexible, reconfigurable, benchtop toolbox with state-of-the-art detection and analysis features to enable scientists to pursue and solve scientific questions that require analysis of heterogeneous cell populations. The microsystem modules are used for real-time quantitative assessment of expression of different genes and the resulting phenotypes as a function of environmental (and cell-to-cell) interactions. The MLSC progress to date includes the development of microsystems with multiple sensors, environmental control, and cell manipulation capability. To ensure broad applicability, experiments have been performed with yeast, macrophages, T-cells, and bacteria. Current capabilities in live cells include measurement of substrate-dependent O₂ consumption rates and measurement of expression from multiple genes using fluorescent reporters, while in fixed cells we are developing the ability to carry out qPCR and qRT-PCR on multiple genes simultaneously and to generate single cell proteomics profiles.

As we expand technology capabilities, we are focusing this technology on a set of interconnected problems involving in situ cellular heterogeneity that link genomics to phenotype to health. These interrelated challenges all have the common theme of pathways to cell damage and cell death and include pro-inflammatory cell death (pyroptosis), programmed cell death (apoptosis), and avoidance of cell death (neoplastic progression). The disease states represented by this suite of problems include cancer, heart disease, and stroke.

3. Career Path

My philosophy in work is to be aware of what is going on around me, to learn as much as possible, and to recognize and take advantage of opportunities when they arise. This requires risk and change but that is where new discoveries are made.

In high school I wanted to be an architect and would stay up all hours of the night working on designs and models of new houses. Right after my junior year in high school, I participated in the Junior Engineering Technical Society (JETS) program and the Women in

Engineering (WIE) program at the University of Idaho where I learned computer programming and was introduced to the various engineering disciplines. This new discovery combined with my interests in architecture and math led me to major in civil engineering with an emphasis on structures as an undergraduate student at the University of Washington.

During my undergraduate years I participated in three 6-month engineering co-op programs—one at the Puget Sound Naval Shipyard in Bremerton, Washington, and two at the NASA Johnson Space Center in Houston, Texas that included training of the Space Shuttle astronauts on the Shuttle Mission Simulator. It was through these invaluable work experiences that I gained appreciation for my coursework at the university and discovered that with training in electrical engineering I could do research in robotics and control systems. I went on to obtain a masters degree in Electrical Engineering at Rensselaer Polytechnic University and a Ph.D. at Stanford University. Inbetween my M.S. and Ph.D., I worked as a member of the technical staff at the Jet Propulsion Laboratory testing flight hardware and software for the Galileo spacecraft and on the design of large flexible space structures. My M.S. and Ph.D. theses were on robotics and control systems.

Upon joining the University of Washington as an Assistant Professor of Electrical Engineering in September 1992, I worked with faculty in the new Department of Molecular Biotechnology. The Human Genome Project was underway and they needed robotics and automation to speed up the processing of DNA sequencing. I immersed myself in genomics training by working in the Molecular Biotechnology laboratories, attending seminars, taking courses, and so on while I started the Genomation Laboratory in Electrical Engineering. I was funded on a Special Emphasis Research Career Award through the National Institutes of Health, National Human Genome Research Institute, to train in genomics and to apply my expertise in robotics and control systems. This interdisciplinary training has yielded much fruit as I have now worked in automation for genomics for 13 years.

More recently, I learned about a new effort called NEPTUNE (<http://www.neptune.washington.edu>) to place a cabled underwater observatory on the Juan de Fuca plate in the northeast Pacific Ocean to take measurements in time and space to fully understand ocean

and earth processes. We are taking the research in the Microscale Life Sciences Center and developing it further into ecogenomic sensors that will monitor the microbial environments on the seafloor and in the water column.

In January 2007, I will become Dean of the Ira A. Fulton School of Engineering at Arizona State University. One of the primary goals is to train transdisciplinary engineers and to engage them in research across campus including earth and space exploration, sustainability, and biodesign as well as business, design, and the arts.

References

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Deirdre Meldrum

Deirdre Meldrum, Ph.D. received the B.S. in Civil Engineering degree from the University of Washington, Seattle, WA in 1983, the M.S. in Electrical Engineering degree from Rensselaer Polytechnic Institute, Troy, NY, in 1985, and the Ph.D. in Electrical Engineering degree from Stanford University, Stanford, CA, in 1993. She is currently a Professor and Director of the Genomation Laboratory in the Department of Electrical Engineering, Adjunct Professor of Mechanical Engineering at the University of Washington, Seattle, WA. Her research interests include genome automation, microscale systems for biological applications, ecogenomics, robotics, and control systems. Dr. Meldrum is a member of AAAS, ACS, AWIS, HUGO, IEEE, Sigma Xi, and SWE. In 2003, Dr. Meldrum became a Fellow of the American Association for the Advancement of Science (AAAS) and in 2004, a Fellow of IEEE. She will become the Dean of the Ira A. Fulton School of Engineering at Arizona State University, Tempe, Arizona, in January 2007.