Illumina, Inc. Research and Technology Development Scientific Seminar

Automated microfluidic pumps and valves for interfacing miniature bioreactors to analytical instruments: organ-on-chip and microphysiological systems perfusion controllers, microclinical analyzers, well plate microformulators, and robot-scientist microchemostats

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In their early days, lab-on-a-chip devices apocryphally required a detector-on-a-truck. That said, today's high-throughput screening (HTS) with well plates currently utilizes massive robot arms with the capability of injuring or even killing the humans who operate and service them. The standard three-step HTS paradigm of culture, expose, and measure in more than 1000 wells per plate severely limits the options in timing the delivery of drugs, reagents, and toxins and the withdrawal of samples for time-series analyses, and cannot replicate circadian rhythms or realistic pharmacokinetics. Perfused organoids, organs-on-chips, and coupled microphysiological systems present a completely different set of high-content screening challenges: Smaller numbers of more complex experiments that run for days to weeks require physiologically realistic media volumes and flow rates that are often delivered by gravity, syringe pumps, pressurized reservoirs, or on-chip peristaltic pumps, and are studied with high-content imaging and untargeted transcriptomics and mass spectrometry. Single-cell analyses clearly benefit from on-chip pneumatic microfluidic pumps and valves that control nanoliter volumes, but these technologies do not scale well to the hundreds of microliters required to maintain cell populations that are large enough for application of untargeted transcriptomics, proteomics, and metabolomics, including engineered tissue constructs and steady-state microbial chemostats. Since 2001, the Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE) has been focusing on the development of compact, low-cost, intermediate-scale, multichannel microfluidic pumps that deliver microliters per minute, simple microfluidic valves that can control a hundred fluidic channels with a single motor, and notebook computer digital control of dozens of pumps and valves over WiFi. The goal is to shift from bringing a well plate to a single, large, fixed robot to bringing a smaller robot to the well plate, at a cost that would enable hundreds if not thousands of parallel, independent experiments.

These technologies have been demonstrated with a human neurovascular unit that models the blood-brain barrier and the neurons it protects, and an engineered cardiac tissue construct, both populated with cells differentiated from patient-derived induced pluripotent stem cells. A combination of a pump with multichannel valves and a multichannel electrochemical sensor created an automated, self-calibrating MicroClinical Analyzer for tracking cellular metabolic and neurotransmitter activity. A MultiWell MicroFormulator that won an R&D 100 Award allows pharmaceutical companies to apply different pharmacokinetic drug profiles to each well in a plate and replicate *in vivo* cellular responses and tumor growth rates, and will soon enable *in vitro* studies of complex circadian rhythms. In recognition of the analytical advantages of steady-state bioreactors over those that are fed every day or two, VIIBRE is combining many of its technologies to create for Ross King of Chalmers University of Technology a 10,000-channel automated microchemostat that will operate as a robot scientist named Genesis and perform hundreds of thousands of independent, optimally designed experiments with online mass spectrometry readout. Given their low cost, modular design, rapid prototyping, advanced state of development, WiFi control, possible fabrication from non-PDMS materials, ease of replacement of fluidics, and ability to perform large numbers of different fluidic operations, the VIIBRE pump, valve, control, and analytical technologies should be applicable to a broad spectrum of commercial and research applications.