VIIBRE Research and Publications

The Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE) has established since its founding in 2001 a broad program to develop and utilize a variety of BioMicroElectroMechanical Systems (BioMEMS) devices and advanced instrumentation to address pressing questions in integrative biology. The focus has been on devising novel micro- and nanosystems and techniques that enable measurements on biological systems that have previously been either impossible or difficult to do with high throughput. The work frequently targets the dynamics of biophysical and physiological processes. The first major VIIBRE effort in this area has been led by the Cliffel group to design, optimize and apply advanced multianalyte electrochemical sensors in MicroPhysiometers to determine the effects of chemical and biological toxins on metabolic dynamics.[1-8] Their work now includes electrochemical detection of insulin[9] and single-cell scanning electrochemical microscopy (SECM).[10] VIIBRE's measurements of metabolic dynamics have been extended to nanoliter and picoliter volumes by the Baudenbacher group with custom NanoPhysiometers with microfabricated electrochemical sensors[11-16] to study cardiac excitation-contraction coupling in single cardiomyocytes,[17-19], PicoCalorimeters[20,21] that are now being applied to the study of cellular metabolism and biochemical reactions, and pulse-delivery microfluidics for cellular signaling.[22] The Wikswo group is developing a dynamic amino-acid flux analyzer[23], and devices for long-term culture of small populations of cells in NanoBioreactors[24-26] and for the growth of cultured cardiomyocytes during electrical stimulation.[27] A major effort is underway, as a collaboration between the Wikswo, McLean, Cliffel, and Baudenbacher groups at Vanderbilt, the Lipson group at Cornell, and the Jenkins group at CFD Research Corporation, to apply symbolic regression, machine learning, electrochemical and optical sensing, and nanoelectrospray ion-mobility mass spectrometry to infer the equations underlying metabolic and signaling dynamics.[28-32]

Several different classes of microfluidic and other devices are being developed by VIIBRE faculty, staff and students for the study of chemotaxis and haptotaxis in cultured cells,[33-39] cellular forces,[40-44] predator-prey dynamics in bacteria-protozoal communities maintained in microfabricated environments,[45,46] nanoprobes as reporters of the time-dependent expression of cell surface receptors,[47] metabolic oscillations in pancreatic islets,[48-50] protein binding and configuration control in support of fundamental studies of haptotaxis,[51] and the dynamics of inter- and intracellular signaling during the immune response in non-adherent immune cells and immune cell pairs restrained by massively parallel arrays of microfabricated traps.[52] Electrical stimulation has been used to control cell fate,[27] and VIIBRE's microfluidic devices are being applied in the tracking of differentiation of stem cells[53] and apoptosis of cancer cells.[54] A variety of broadly applicable microfluidic and optical techniques support these efforts. [55-59] Image processing is providing new tools for studying cell motility and mechanical activity,[60] and mathematical modeling is inspiring new research directions.[61] VIIBRE has supported tissue engineering research in the Shastri group[62-71] and anticipates extending this research in new directions in the immediate future.

Shane Hutson is using advanced optics and microfluidics to study *Drosophila* and *C. elegans* morphogenesis and wound healing[72-76] (supported by an NSF career award) and laser tissue ablation.[77-80] The Baudenbacher group has developed ultrahigh resolution scanning superconducting quantum interference device (SQUID) microscopes[81,82] for studies of algal[83] and mammalian electrophysiology,[84] cell sorting,[85] and geomagnetism.[86-88] All of these studies are part of a larger effort to develop devices and models that will enable the "instrumentation and control" of single cells and small populations of cells, and to thereby eventually probe the complexities of systems biology.[89,90]

At the larger scale of the isolated mouse and rabbit heart, a collaboration between the Baudenbacher, Sidorov, and Wikswo groups and Dr. Richard Gray of the Food and Drug Administration is utilizing advanced electrical, magnetic,[82,84] and optical[91,92] measurements, stimulators[93-95] and image processing[96,97] to explore the connection between cardiac electrophysiology, metabolism, and heart disease.[98-103] The SQUID imaging work has been extended to include magnetic measurements of gastrointestinal electrical activity.[104,105] By supporting key faculty recruitments, VIIBRE helped strengthen functional magnetic resonance imaging at Vanderbilt.[106]

VIIBRE has an active program in undergraduate research, the Systems Biology and Bioengineering Undergraduate Research Experience (SyBBURE), funded by the Vanderbilt alumnus Gideon Searle. The Searle-SyBBURE program, directed by Kevin Seale, is a year-round, multiyear program in which twenty undergraduates from across the entire university are trained in microfabrication and cell biology, and work with graduate students, postdocs, faculty, and staff with the objective of developing their own, independent research projects.[107]

VIIBRE research, which spans molecules, cells, tissues, and organisms, has been funded in part by the NIH, DOD, Whitaker Foundation, NSF, Human Frontier Science Program, and industry. These and related efforts that have not yet led to publications or external funding are the result of active, multidisciplinary projects already established between VIIBRE and collaborating faculty, and will provide key components of the technical foundation for many of the projects at the intersection of medicine, biology, engineering, and the physical sciences.

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