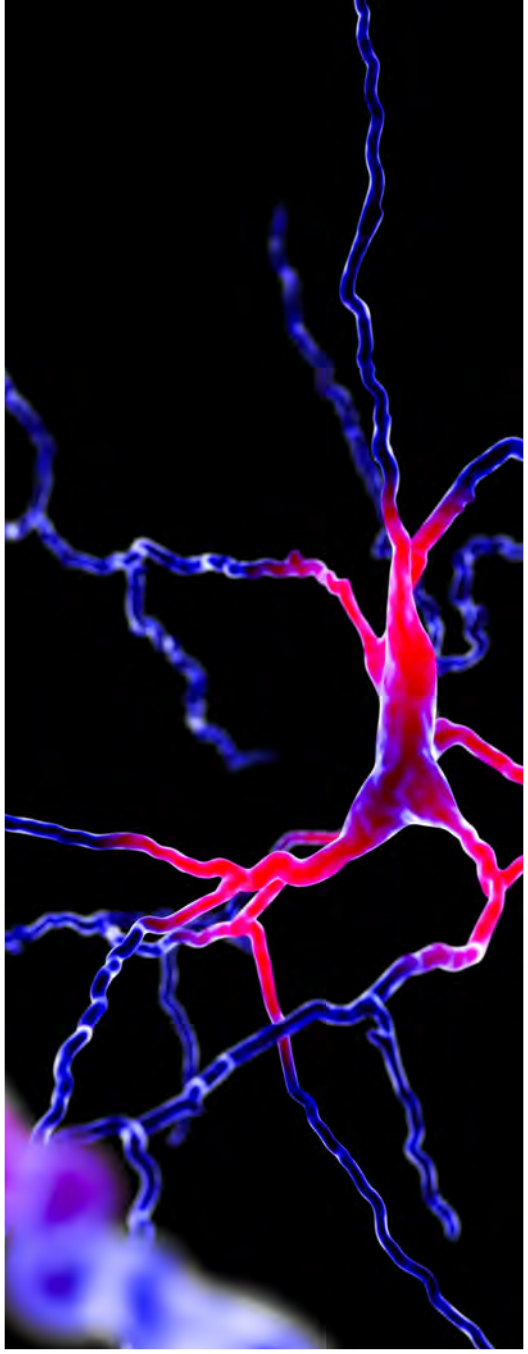


KANSAS STATE
UNIVERSITY

INTEGRATED MICROFLUIDIC DEVICES

Integrated microfluidic devices

Integrated microfluidic devices have become very versatile tools for biological and biomedical investigations. Devices capable of single-cell analysis (SCA) have proven useful in the study of the etiology of several chronic diseases including cardiovascular disease, neurodegenerative diseases, and cancers. The Culbertson and Bossmann research groups at Kansas State University have been developing automated SCA microfluidic devices that have focused on the minimization of peripheral equipment in terms of footprint as well as cost. The first major step made toward miniaturization was achieved through the development of on-board peristaltic pumps. Traditionally, microfluidics requires some external pumping device (e.g. syringe pump) to generate flow, however, they tend to be rather bulky and offer limited real-time control of flow rates. Using an array of Quake-style pneumatic valves controlled by a $5 microcontroller connected to a $4 driving circuit (figure 1), continuous flow is generated within the device. The flow rate can be increased or decreased by simply adjusting the actuation pressure using a small compressed air regulator.

More recently, efforts have been directed toward maximizing the capabilities of the optical detection system by integrating a multi-mode optical fiber (MMF) to enable simultaneous detection at two points of interest within the device. Previously, incorporation of multi-point detection required duplicate optical components including an objective, alignment mirrors, possible another excitation source and most importantly an additional detection system. The cost of the detection system alone runs into the thousands. Beyond the cost, there are also spatial constraints on how close two

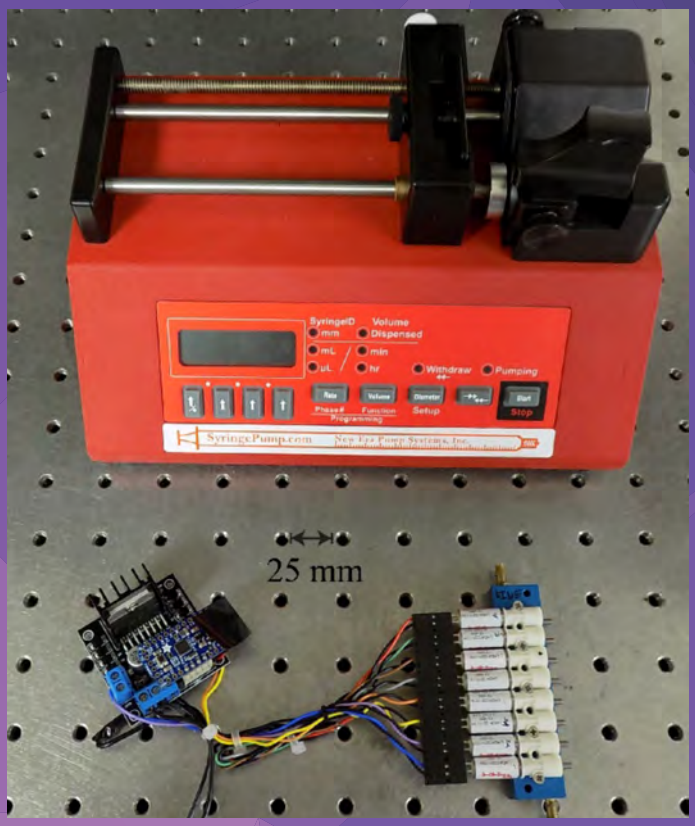


Figure 1. A photograph of a syringe pump (top) next to the miniaturized pump control electronics (bottom).

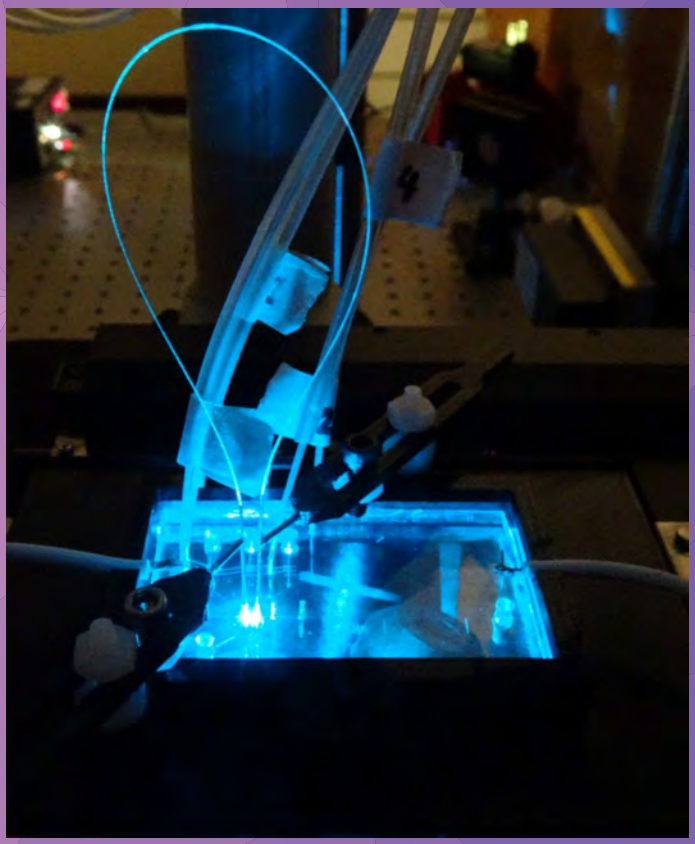


Figure 2. A photograph of the MMF bridge integrated into the microfluidic SCA device. The device is mounted to the microscope stage using a custom designed 3D printed holder.

objectives may be which may be problematic considering the compact designs of microfluidic devices. The configuration of the MMF integrated in the device can best be described as a bridge (depicted in figure 2). Both ends of the MMF are aligned with different points within the fluidic manifold of the device. One end is coincident with the laser induced fluorescence (LIF) detection spot of the electrophoretic separation channel with the excitation light being directed into the fiber. The excitation is then transmitted through the bridge to the second spot under which fluorescently labeled cells flow by. The fluorophores within the cells are then excited and emit fluorescence, which is subsequently transmitted back through the bridge, out of the other end of the fiber and into the same detection system used for the electrophoretic separation. Each end of the MMF occupies a total footprint of around 600

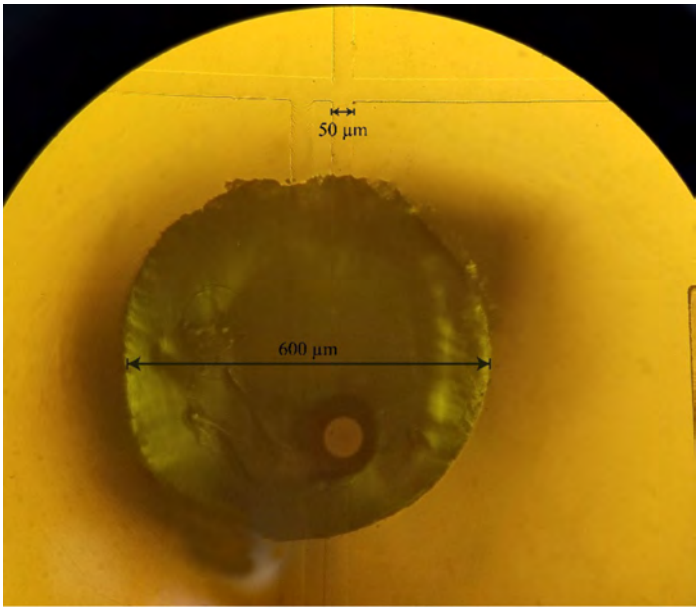


Figure 3. A photograph showing the footprint of one end of the MMF bridge (600 µm) relative to the microfluidic channels (50 µm).

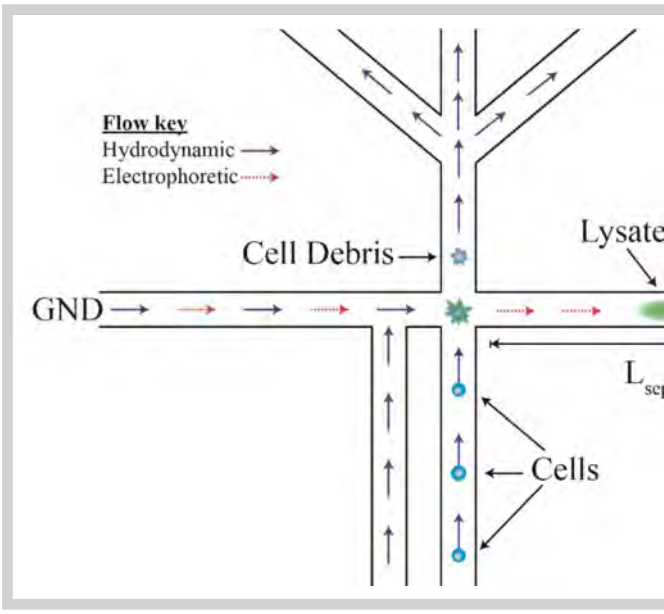
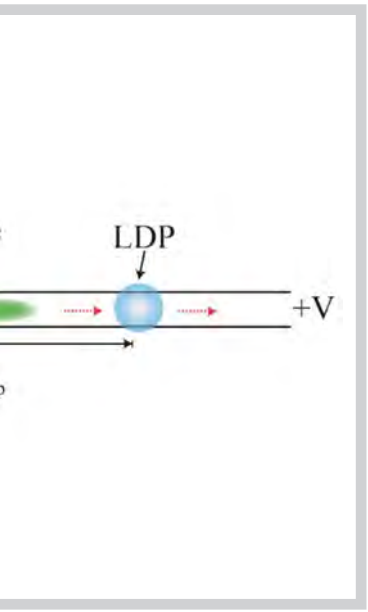


Figure 4. A diagram illustrating the working princip
device. Lsep indicates the length of the electrophor

microns (figure 3) in the device, yielding a total footprint of less than 1.5 mm total. At a length of approximately 10 cm and a cost of less than $4 per meter it is clear to see why the integrated MMF is an incredibly attractive alternative to more traditional optical strategies.

Within the context of our SCA microfluidic device, the integration of the MMF bridge has dramatically increased its analytical capabilities. The device functions by continuously drawing labeled cells toward the separation channel whereupon they experience a high electric field and are electrokinetically lysed. The intracellular contents are then injected into the separation channel, electrophoretically separated and finally detected via LIF. A diagram illustrating the working principles of the device is shown in figure 4. Typical analyses often require us to label cells with more than one fluorescent probe. Our previous optical configuration did not allow us to detect when a cell was entering the lysis intersection making it difficult to confidently assign fluorescence peaks to individual cells and limiting the practical number of analytes per cell that we could measure simultaneously. Attempting to quantify more than 3 analytes would likely result in an incomprehensible electropherogram. Using the MMF bridge, we chose to place the second detection spot just below to the intersection so that we may detect when a cell is about to lysed. We use this “intact” cell signal as a starting time for the electrophoretic separation. An example electropherogram showing the intact cell signal and two fluorescence peaks is depicted in figure 5. We can now label cells with more probes than before which may enable us to simultaneously measure enzyme activities across multiple cellular pathways. In drug development as well as the burgeoning field of personalized medicine, it is crucial to rapidly and comprehensively study the effects of drugs on cells and cellular processes. It is therefore our goal that in the future our device can be used for those purposes.



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retic separation.

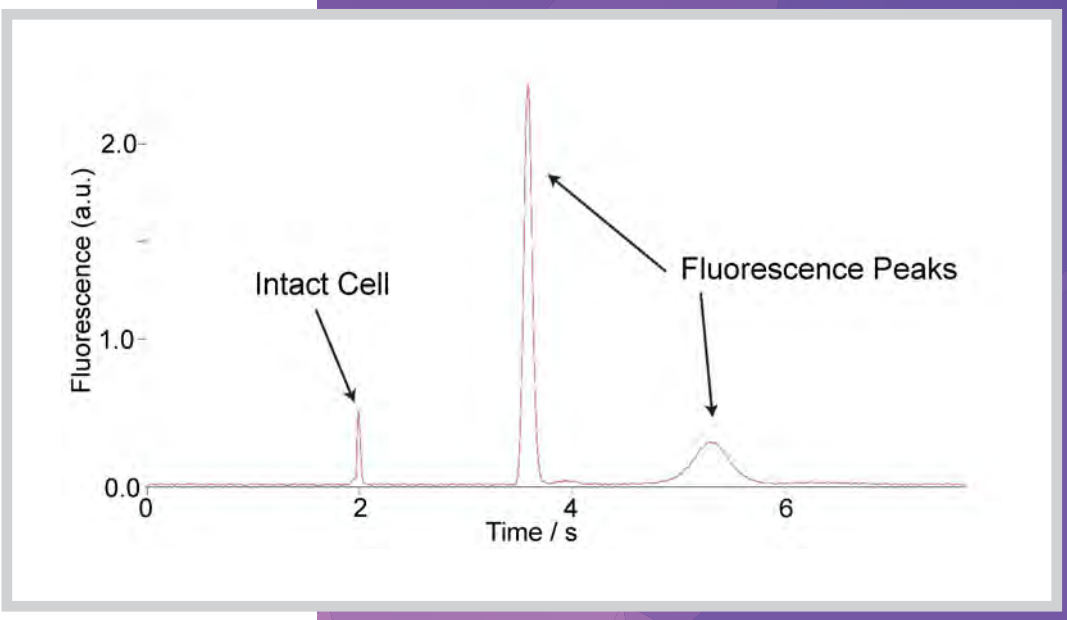

Figure 5. An example electropherogram showing the intact cell signal and two fluorescence peaks.

"In drug development as well as the burgeoning field of personalized medicine, it is crucial to rapidly and comprehensively study the effects of drugs on cells and cellular processes. It is therefore our goal that in the future our device can be used for those purposes."

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Advancing basic chemical research while developing a globally competitive workforce

Carol Bessel and Melissa Olson from National Science Foundation's Division of Chemistry (CHE) reveal the organisation's goal of advancing basic chemical research while also developing a globally competitive workforce

The Division of Chemistry (CHE) at the National Science Foundation is committed to the goal of advancing basic chemical research while also developing a globally competitive workforce. The pursuit of fundamental chemical science, however, is not just bound to the lab. Rather, it serves to address and solve some of the most pressing societal challenges.

CHE actively solicits and funds projects that design and develop sustainable chemistry pathways from synthesis to recycling; advance algorithms and novel qubit structures for quantum computing; accelerate and complement chemical discovery with data mining and artificial intelligence (AI); and seek to understand and engineer the biochemistry governing life processes such as in synthetic biology, epigenetics and studies of the microbiome. Because each of these grand challenges straddles disciplinary lines and national borders, CHE also promotes interdisciplinary and international teams. Any real solution to these grand challenges also requires public support, calling chemists out of the lab to communicate, interact and broaden participation.

Chemistry forms the basis of nearly all consumer products, from the long, messy chains of carbon atoms in plastics, to the atomically precise molecules in pharmaceuticals with chiral structures. While these products prove incredibly useful and sometimes lifesaving, their entire 'life cycle', from cradle to grave to cradle, must be considered. The desirable durability of plastics leads to their problematic persistence in the environment, as witnessed in plastic 'islands' in the oceans. Aiming to reduce plastics in the environment, CHE funds projects exploring catalysis for novel polymers designed to be chemically or mechanically degraded, biodegraded and/or upcycled into new consumer goods. The atom-level precision required in fine chemicals often leads to many-step reactions and purification processes, each consuming energy or generating solvent waste. Creating sustainable synthetic methods, real-time characterisation and facile separations are priorities for CHE. Organic electrosynthesis is an especially opportune area for collaboration, especially with engineering partners such as the Division of Chemical, Bioengineering, Environmental and Transport Systems (CBET) Division at NSF. CHE also hopes to strengthen this field through international partnerships in the future.

"One of the first, large-scale projects to develop and adopt big data concepts was the Human Genome Project. Sequencing the human genome was a momentous achievement, but it also raised a myriad of additional, interesting scientific questions."

While developing sustainable chemistry is imperative, fundamental research underpins all advances. This includes the particle-to-particle and atom-to-atom interactions defined by quantum mechanics. Through Quantum Leap, one of NSF's Big Ideas to guide the next decade of research, CHE supports research addressing and exploiting a wide variety of quantum phenomena, from spectroscopy with entangled light to

controlling electronic spin for molecular qubit design. This work blurs interdisciplinary lines and requires a new approach to workforce development, so CHE partners with eight other NSF divisions for projects such as QISE-NET, which builds 'Triplets' between students, academic mentors and industrial mentors and Quantum Leap Challenge Institutes, large-scale interdisciplinary research projects that seek to advance the frontiers of quantum computation, communication, simulation and/or sensing.

While the development of quantum computing harnesses the smallest of phenomena, chemists are also turning to big data. With the generation and assemblage of mass amounts of computational and experimental data, exploration of new chemistries can be guided and accelerated with tools such as data mining, machine learning and cheminformatics. CHE supports the development and application of these tools through the Data-Driven Discovery in Chemistry program and through the Harnessing the Data Revolution Big Idea. These projects touch all fields in chemistry, from the optimization of chemical reactions in microdroplets to the search for protein folding guidelines. These techniques can require programming and statistical analysis that go beyond the bounds of traditional chemistry. To foster new collaborations between mathematicians and chemists, CHE has worked with the Division of Mathematical Sciences to sponsor an Innovation Lab bringing together investigators from both disciplines to innovate and generate new ideas and project proposals.

One of the first, large-scale projects to develop and adopt big data concepts was the Human Genome Project. Sequencing the human genome was a momentous achievement, but it also raised a myriad of additional, interesting scientific questions. Another NSF Big Idea, Understanding the Rules of Life, aims to tackle one of these questions – how to predict phenotype (observable characteristics) from genetic information. CHE plays a significant role in answering this question, especially as it is reduced to molecular interactions and chemical responses. These projects include designing platforms for the study of macromolecules that reproduce the crowded conditions in cells and synthesizing artificial organelles, both of which are co-funded with CBET or the Directorate for Biological Sciences.

While poised to address the scientific aspects of these challenges, chemistry needs an informed and active public to help fund or implement any solution. Every award that CHE makes requires investigators to consider the broader impacts of their work, which includes the impacts on the public. Chemistry encourages investigator efforts aimed at education, for example, Energy and U, a collaboration between the chemistry and theatre departments at the University of Minnesota that teaches students about the laws of thermodynamics. Other investigators develop entirely new media for education, such as 3D printed protein structures to help teach blind students about protein dynamics. CHE also encourages chemists to engage in efforts outside academe, offering support for graduate students to pursue internships in industry or government laboratories.

Though CHE strategically supports the programs and initiatives mentioned above, it continues to support basic chemical research of all kinds. Chemistry remains a powerful tool, both inside of the lab when exploring fundamental phenomena and beyond the lab, improving the world around us.

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“Our faculty is dedicated to doing world-class chemistry here in the heartlands. Our professors aim to train new generations of scientists who will be the leaders of tomorrow in research, teaching, medicine and industry.”

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