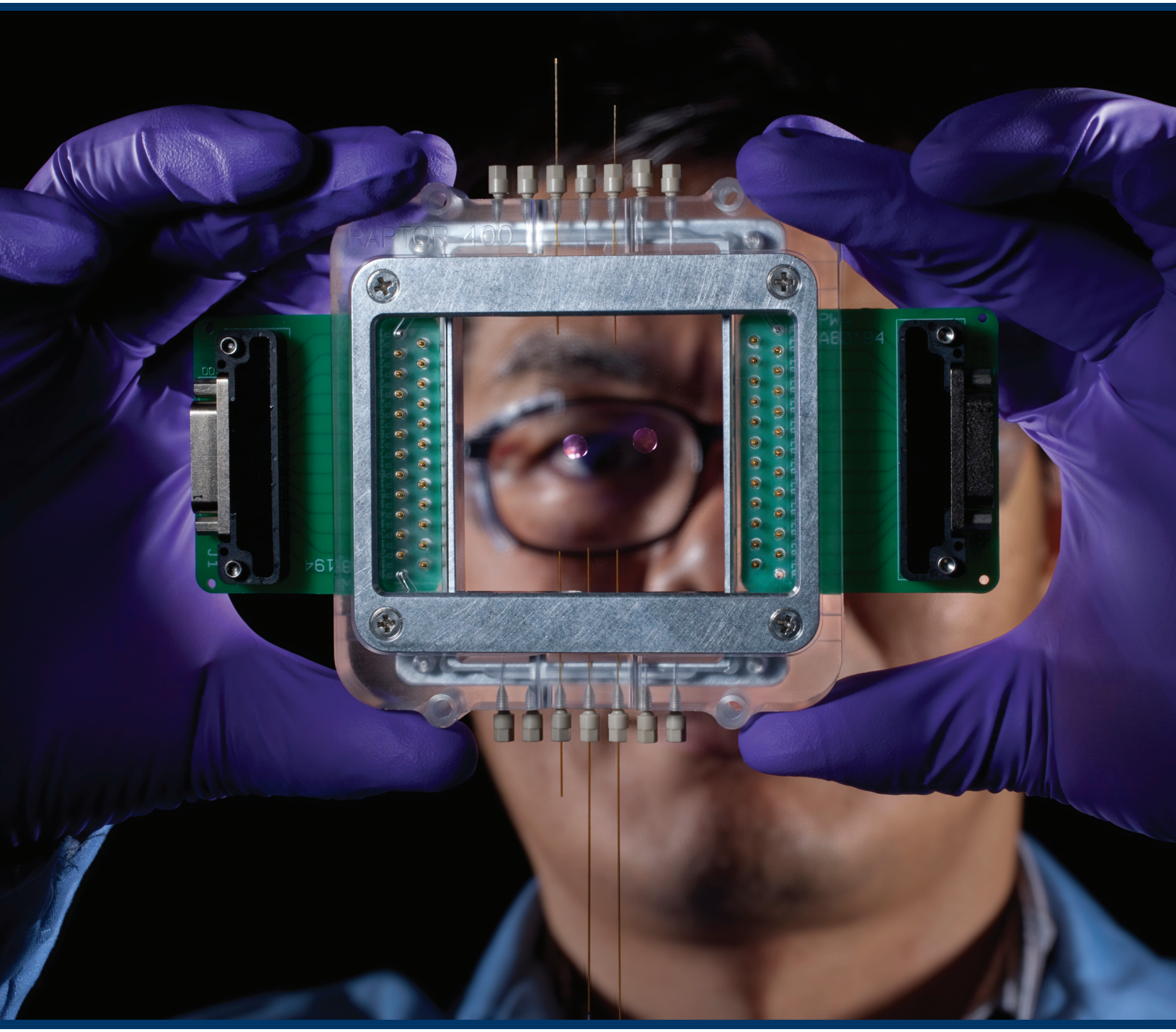
SAND2012-2105P

Sandia Digital Microfluidic Hub



Sandia Digital Microfluidic Hub

1. Developer Information

A. Primary submitting organization

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2. Product Information

A. Product name

Sandia Digital Microfluidic Hub

B. Product photo

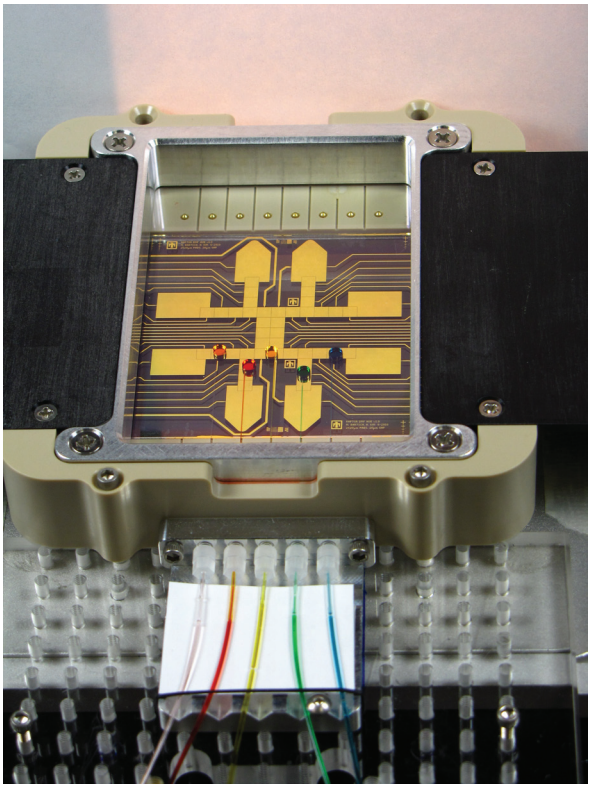

Figure 1: Color droplets dispensed through capillary interfaces filled with dye solutions onto the Sandia Digital Microfluidic Hub.

3. Brief Description

The Sandia Digital Microfluidic Hub — a droplet-handling router — enables the interconnection of diverse processing and analysis modules to automate complex microliter-scale molecular biology sample-preparation protocols.

4. First Marketed

The Sandia Digital Microfluidic Hub was first available for licensing and external evaluation in mid-2011. Technical advance SD#11945, "Digital Microfluidic Platform and Method for Interface," by Michael Bartsch, Mark Claudnic, Jim He, Hanyoup Kim, Kamlesh Patel, Ron Renzi, Jim Van de Vreugde, was submitted internally to Sandia's Partnerships, Agreements, and Licensing System February 23, 2011.

5. Has this product or an earlier version been entered in the R&D 100 awards competition previously?

No.

6. Principal Developers

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7. Product Price

The Sandia Digital Microfluidic Hub, including its electrode-switching power supply and graphical user interface control software, costs less than $3,000 per unit based on current low-volume production approaches. In higher production quantities, we estimate this base unit cost would be reduced to $1,000. As currently manufactured in-house at Sandia, the reusable and/or semi-consumable electrode-patterned glass digital microfluidic substrates cost approximately $50-$75 each. Produced at scale outside Sandia, we estimate the cost per substrate could be less than $5.

Uniquely enabled by the capabilities of the Sandia Digital Microfluidic Hub, the integrated automated molecular biology (AMB) system described below for performing the Nextera™ next generation sequencing library preparation protocol costs about $6,500 based on current low-volume implementation (detailed in Table 1). Assuming economies of scale in larger-volume production, the cost of this system is estimated to be approximately $4,000.

Table 1: Cost Breakdown of the Sandia Digital Microfluidic Hub-based Nextera™ Library Preparation System (as currently implemented based on low-volume production and use of commercial off-the-shelf [COTS] hardware)

Item	Quantity & Unit Price	Subtotal
Sandia Digital Microfluidic Hub (including electronics and software)	1 × $3,000	$3,000
Digital microfluidic substrates	2 × $50	$100
OEM syringe pumps with multiport valves	2 × $1,200	$2,400
COTS thermal cycling system	1 × $600	$600
Custom enzyme microreactor	1 × $250	$250
Custom magnetic bead capture module	1 × $100	$100
COTS fittings, capillary tubing, etc.	Various	$50
Total		**$6,500**

8. Patents

Provisional patent US 61/478,641 was submitted April 25, 2011. As of February 2012, full patent application is in preparation.

9. Primary Function

While microfluidic techniques have long been viewed as a promising alternative to the expense and sample volume limitations of pipette-based automation, the complexity of molecular biology protocols have so far largely defied such solutions. The perennial vision of monolithically integrated “lab-on-a-chip” systems has proven particularly problematic in the sample-preparation arena, as no one microfluidic technology (e.g., chip-based channel microfluidics, flow-injection analysis microfluidics, electrowetting-on-dielectric digital microfluidics, multiphase droplet microfluidics) has been able to effectively replicate the diversity of operations required by these molecular biology protocols.

To address the challenges and limitations of current molecular biology automation options, our Sandia team has developed a novel Digital Microfluidic Hub (Figure 1) that enables modular — as opposed to monolithic — microfluidic integration solutions to complex sample preparation workflows. Our Digital Microfluidic Hub capitalizes on the unique features and benefits of digital microfluidic technology by innovating in the key area that has until now limited broader real-world applications: connectivity.

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Digital microfluidic (DMF) technology uses electrostatic and electrowetting forces to manipulate microliter-scale droplets sandwiched between closely spaced, hydrophobically coated substrates patterned with arrays of individually addressable electrode pads. By selectively applying voltage sequentially to these stepping stone-like electrodes, droplets can be moved in discrete, stepwise fashion along the electrode-defined pathways. Droplet operations such as merging, splitting, mixing, and aliquotting can also be performed at microliter volume scales much smaller than those accessible to conventional pipette-based techniques.

The Sandia DMF Hub effectively replicates the function of a pipetting robot in a high-throughput laboratory automation workflow, but at a fraction of the size, cost, and complexity.

Figure 1 shows perhaps the most powerful connectivity feature of the Sandia DMF Hub, the in-plane capillary interface. With capillary tubes fixtured between the two digital microfluidic substrates, this unique interface provides the means to directly couple the interior of the DMF Hub and its discrete droplet manipulation capabilities to external fluid handling elements (i.e., pumps and valves), as well as to off-hub sample processing or analysis modules. The inherently low volume of the in-plane capillary interconnects enables fluidic transfers at microliter and even sub-microliter volumes, meaning that small, concentrated samples need not be diluted for transport or mixing as in many pipette-based bench-top processes.

Moreover, the seamless nature of droplet-to-capillary fluid transfer means that the Sandia DMF Hub can reliably interconvert liquid samples between continuous flow, segmented bolus flow, and discretized droplet formats with no appreciable volume loss, providing added flexibility in the design or selection of sub-modules and in their modes of operation. The uniquely freeform fluid handling capabilities of the digital microfluidic array also allow it to effectively bridge the potentially disparate volume requirements of different attached subsystems, a feat virtually impossible to emulate in the small, fixed volumes of pure chip- or capillary-based microfluidic systems. Additionally, because droplets delivered to the Hub can be readily moved, rearranged, and “parked” for extended periods of time, the Hub provides a flexible tool for scheduling, routing, coordinating, and even multiplexing the transport of multiple samples among external processing modules that may have substantially different processing times or duty cycles.

In keeping with the modular — rather than monolithic — integration paradigm described above, subsystems coupled to the Sandia DMF Hub can be individually optimized using the most appropriate technologies, microfluidic or otherwise, to address their particular functional roles. In this way, the unique interface of the Hub enables it to function as a micro-scale fluid distribution router, providing

connectivity and functional integration across a collection of purpose-built sub-modules to implement and automate molecular biology protocols.

In that role, the Sandia DMF Hub effectively replicates the function of a pipetting robot in a high-throughput laboratory automation workflow, but at a fraction of the size, cost, and complexity. It is this capability that sets the Sandia Digital Microfluidic Hub apart from prior attempts at microfluidic laboratory automation, and this capability, enabled by the unprecedented connectivity of the Sandia DMF Hub, that has both attracted interest from industry leaders (Illumina, Caliper, etc.) and garnered a Society for Laboratory Automation and Screening 2011 Innovation Award.

Automated Molecular Biology: the Nextera™ Library Preparation System

To demonstrate the unique capabilities of the Sandia DMF Hub and underscore its applicability to timely, real-world, laboratory automation problems, our team has built and tested an automated molecular biology (AMB) system (Figure 2) designed to perform the Nextera protocol for next generation sequencing (NGS) DNA library preparation. The Nextera AMB library preparation system combines a central Sandia DMF Hub coupled via in-plane capillaries to commercially available fluid handling components and off-hub sample processing modules.

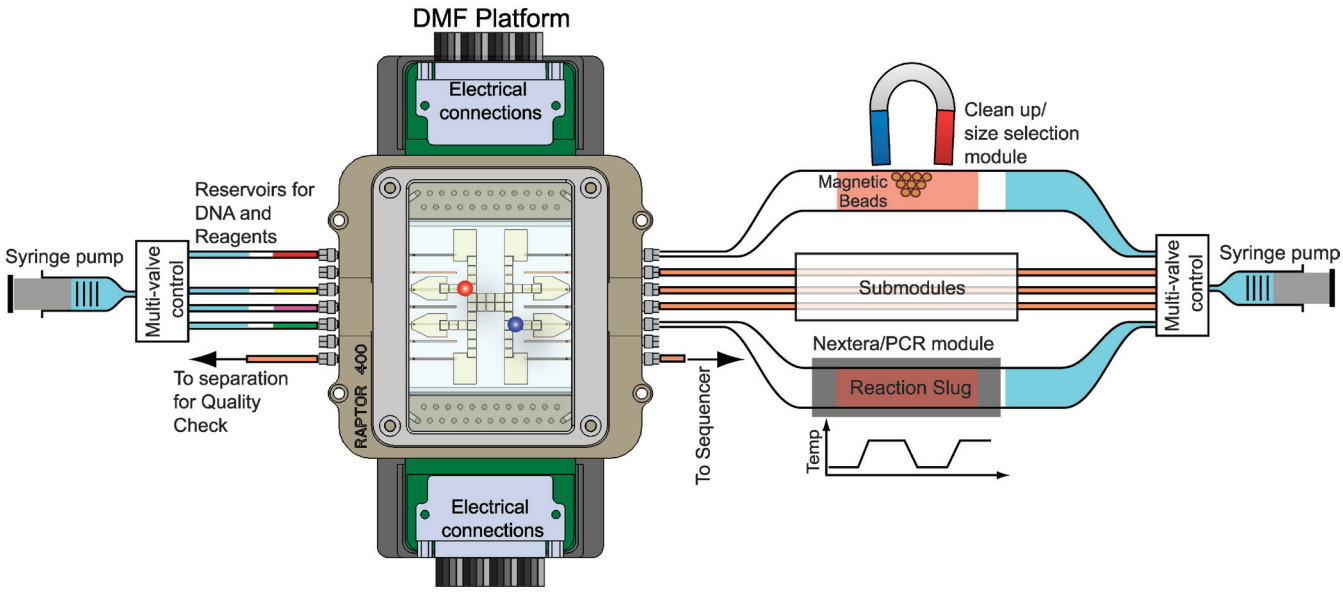


Figure 2: Schematic showing the configuration of the Nextera next generation sequencing DNA library preparation system built around the Sandia Digital Microfluidic Hub.

Two syringe pumps with multiport valves and fluid reservoirs (not shown) are used to deliver sample and reagents to the Sandia DMF Hub and to other capillary-connected sub-modules. These modules include an off-the-shelf thermal cycler

for performing library enrichment by polymerase chain reaction (PCR), a magnetic bead-based DNA size-selection and clean-up module, and a high-temperature enzymatic microreactor module for performing DNA fragmentation. The system also provides the ability to perform a capillary electrophoretic separation directly through one of the in-plane capillaries as a method for providing online quality control monitoring of the library preparation process.

Figure 3 shows the steps involved in executing the full Nextera protocol using the AMB library preparation system — a dramatic validation of the modular Sandia DMF Hub-based approach to small-scale laboratory automation. Further validation of the approach was provided by the successful sequencing of the AMB-prepared library on an Illumina MiSeq© Personal Sequencing System. To our knowledge, this milestone represents the first example of a non-robotic, microfluidic system providing a viable path toward the full automation of next generation sequencing sample preparation.

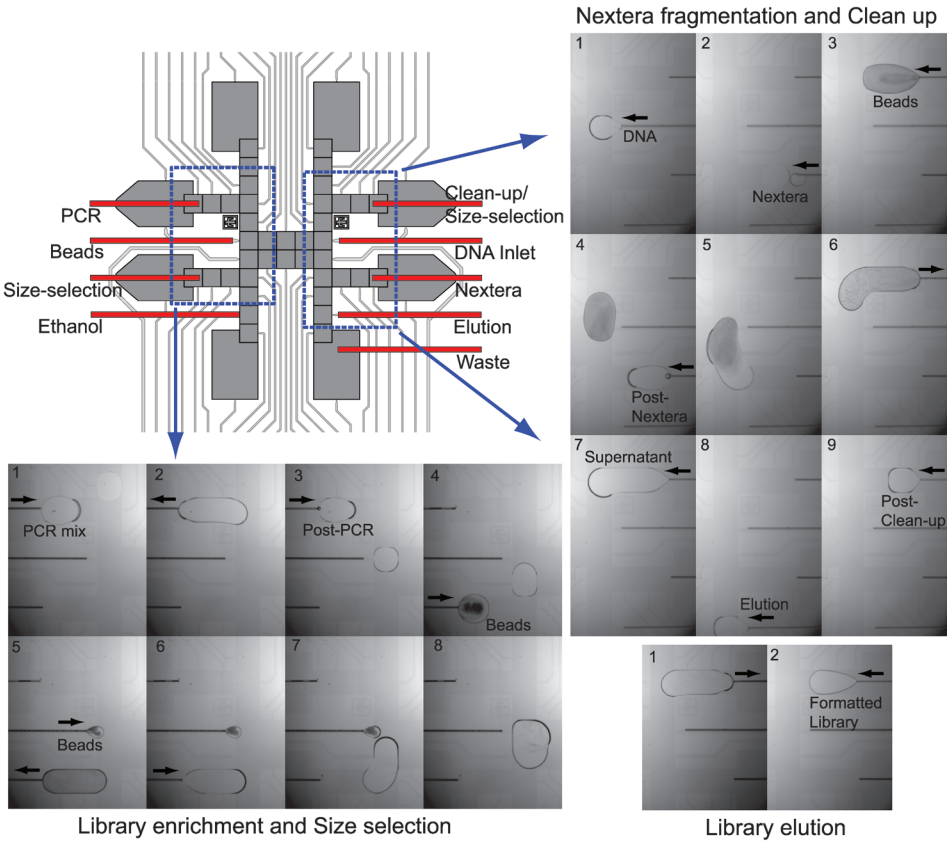


Figure 3: Overview schematic and micrographs showing the steps performed in executing the full Nextera protocol using the automated molecular biology system.

Coupled directly to a MiSeq sequencer, fully automated, and including in situ library validation, the AMB system is expected to execute the Nextera process

in less than half the 4-hour time required for the bench-top protocol and with less than one-tenth the total starting DNA (5 ng vs. 50 ng). Owing to the unique benefits of the Sandia DMF Hub, our Nextera AMB system offers an unparalleled combination of operational flexibility, functional capability, efficiency, cost-effectiveness, and sample-to-answer simplicity, paving the way for the new era of personalized genomics.

10. How It Operates

As described above, digital microfluidic technology, sometimes referred to as electrowetting on dielectric, is a technique for manipulating small-volume droplets on hydrophobic surfaces under the influence of localized electric field gradients and transients. Figure 4 shows a typical cross-section of a closed-format (i.e., lidded) digital microfluidic device of the kind used in the Sandia Digital Microfluidic Hub. Typically, one substrate (bottom) is patterned with an array of individually addressable electrodes that define the paths along which droplets may be moved. This substrate is coated with a layer of insulating material to prevent shorting between neighboring electrodes. The conductive layer on the second (top) substrate is unpatterned, allowing it to function as a ground plane. Both substrates are coated with a hydrophobic layer to increase the contact angle between the droplet and the digital microfluidic substrate, allowing the droplets to move more easily when actuated.

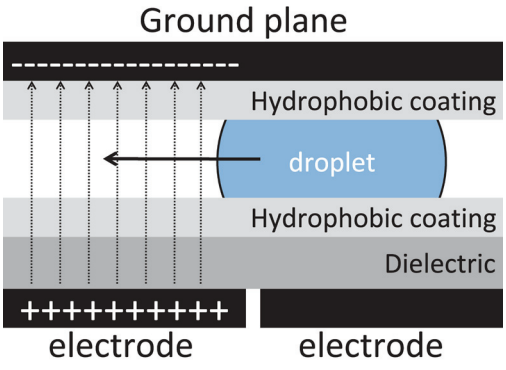


Figure 4: Droplet actuation in a closed-format digital microfluidic device.

In practice, under static conditions all digital microfluidic electrodes are maintained in a grounded state. When droplet actuation is desired, the electrode nearest the droplet in the direction of desired motion is energized (Figure 4), causing the droplet to move stepwise onto the energized pad as a result of a phenomenon called electrowetting. Under the influence of the electric field, the contact angle at the leading edge of the droplet is reduced, and the resulting imbalance in surface tension between the leading and trailing edges of the droplet

produces a net force in the direction of the actuated pad. For the Sandia DMF Hub, droplet actuation is typically accomplished by applying an AC voltage of 50 V_{rms} to 150 V_{rms} at 15 kHz.

11. Building Blocks of Our Technology

Anatomy of the Sandia DMF Hub

Figure 5 shows an exploded assembly view of the Sandia Digital Microfluidic Hub. The primary elements of the Hub are a central manifold frame, two glass digital microfluidic devices (electrode and ground plane), and a pair of outer compression frames.

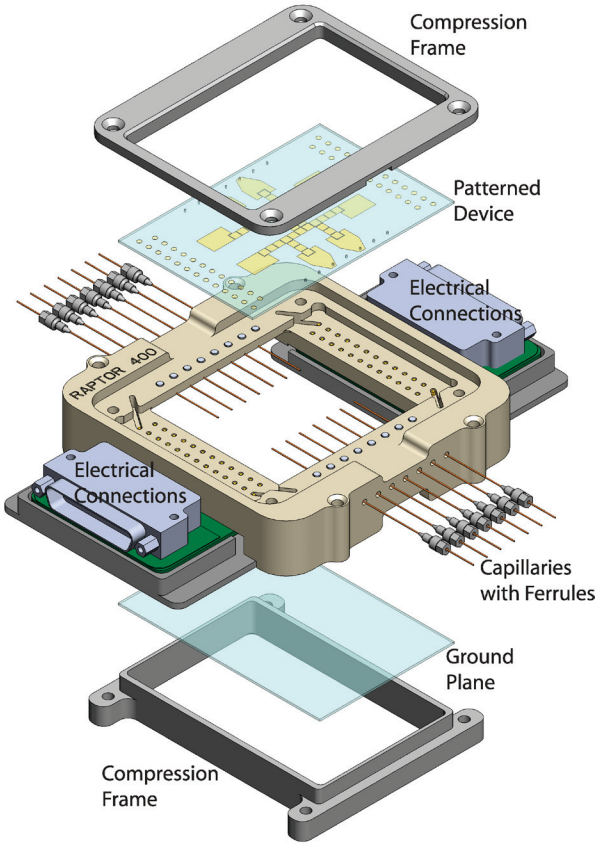


Figure 5: Exploded view of the Sandia Digital Microfluidic Hub with capillary interface.

The manifold frame design embodies the key innovation in our approach to digital microfluidics. Unlike most digital microfluidic designs, which utilize spacer elements (often microscope coverslips or double-stick tape) between their electrode and ground plane substrates, our unique manifold frame provides self-aligning registration of top and bottom digital microfluidic devices to achieve the precise substrate-to-substrate gap spacing required for reliable, reproducible digital microfluidic droplet actuation. With the two compression frames installed, the Hub weighs 90 g and has dimensions of 120 mm × 80 mm × 30 mm (l/w/h).

The novel manifold frame design and open architecture provide a wealth of options for accessing the device fluidically, optically, and electrically.

As depicted in Figure 5, the precision-machined polymer manifold frame has recesses on opposite sides sized to accommodate the 50 mm × 75 mm × 1 mm patterned electrode and unpatterned ground plane substrates. These substrates are fixtured at 90 degrees relative to each other, yielding a 50 mm × 50 mm area of overlap (the droplet usable envelope of the device) with room for electrical connections and mechanical support along the 50 mm ends of each substrate. Substrates are placed in the recesses of the manifold frame with their electrically active, hydrophobically coated surfaces facing inward and are held against registration (datum) surfaces inside the manifold recesses by the aluminum backing frames, providing a fixed substrate-to-substrate gap of 185 µm. As critical as precise substrate positioning is to reliable digital microfluidic performance, the novel manifold frame design and open architecture provide a wealth of options for accessing the device fluidically, optically, and electrically.

Fluidic Interface: In-Plane Capillaries

As Figure 5 shows, the manifold frame is fabricated with a row of seven ports on either side, coinciding with the long sides of the patterned electrode substrate. These ports are centered at the mid-plane of the gap between the two substrates and function as feedthroughs for introducing and precisely positioning capillaries, wires, fiber optics, or other elements into the space between the digital microfluidic substrates. These in-plane components can be swaged in place using standard CapTite™ capillary ferrules and can be left in position even when the top and bottom substrates are installed or removed from the manifold frame. As described above, the ability to fixture in-plane capillaries to provide fluidic access to the device has proven to be a particularly powerful feature, enabling a host of advanced functionalities impossible to achieve with more conventional digital microfluidic designs.

Figure 6 shows how the in-plane capillary interface of the Sandia DMF Hub can be used to transfer small volumes of liquid in or out of the DMF device. For a manifold frame with a typical gap spacing of 185 µm, Teflon®-coated fused silica capillaries with outer diameters of 170 µm or less can be fixed in the interstitial space between the electrode and ground plane substrates. Because the exterior of the capillary is hydrophobic, aqueous liquids delivered through the capillary will initially form a ball at the capillary tip, growing as liquid is added until it is large enough to bridge the upper and lower digital microfluidic substrates. Once the droplet grows large enough to be actuated by the digital microfluidic electrodes, it can be pulled away from the capillary, and moved away for use elsewhere as depicted in the left panel

of Figure 7. Similarly, droplets already on the digital microfluidic array can be actuated into contact with an in-plane capillary and aspirated into it for removal from the device as shown in the right panel of Figure 7.

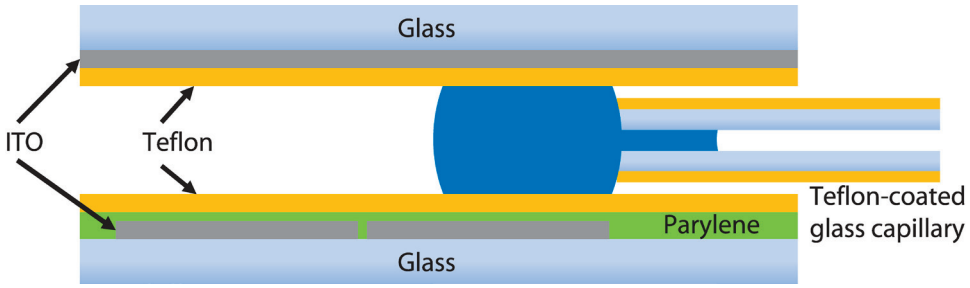


Figure 6: Cross-sectional view of an in-plane capillary dispensing or aspirating a droplet in the space between the digital microfluidic substrates.

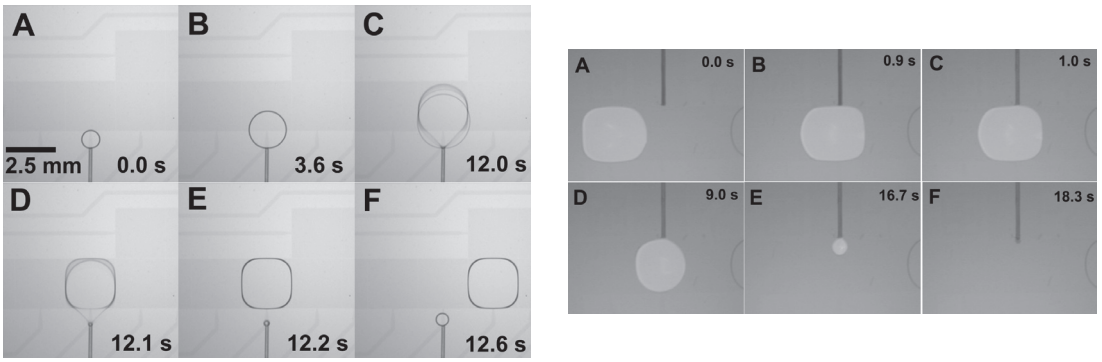


Figure 7: (Left) 2 µL droplet dispensed through a capillary onto the Sandia Digital Microfluidic Hub and actuated away. (Right) 2 µL droplet actuated to the tip of a capillary and aspirated into a capillary.

As Figure 8 illustrates, nanoliter-scale capillary-bound droplets too small to actuate independently on the digital microfluidic array may be cleanly "plucked" off their capillaries by a passing full-size droplet, providing a method for easily obtaining arbitrarily variable mixtures of reagents. In contrast, early digital microfluidic patents devoted considerable space to tabulating the particular number and combination of binary droplet merging and splitting operations that would be required to obtain a droplet with a given dilution of reagent. In conjunction with external syringe pumps, the in-plane capillary interface allows liquid to be transferred to and from the Sandia Digital Microfluidic device with nanoliter precision, providing not only a method for coupling the Hub to external modules, but also the means to execute a variety of advanced on-DMF operations, including serial dilution, droplet sub-sampling, chaotic mixing, fraction collection and sorting, magnetic bead manipulations, and sample archiving. At the other end of the volume spectrum, while most electrode-sized digital microfluidic-droplets are microliters in scale, droplets much larger than an individual electrode pad can

also be manipulated on the device, even bridging continuously pumped inlet and outlet capillaries to enable high-volume fluid transfers.

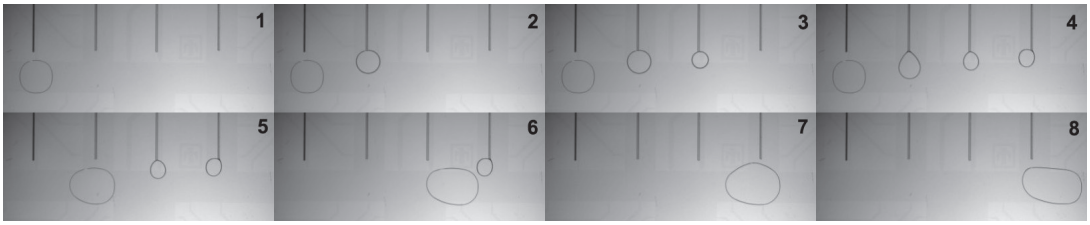


Figure 8: A 2-µL droplet is mixed with three sub-microliter reagent droplets dispensed through capillaries by actuating horizontally along the capillary-interfacing pads.

The in-plane capillary interface allows liquid to be transferred to and from the Sandia Digital Microfluidic device with nanoliter precision.

Fluidic Interface: Through-hole

Beyond the in-plane capillary interface, the Sandia DMF Hub provides additional options for moving liquid to and from the DMF device. One or both compression frames can be replaced with specially designed backing frames providing o-ring seals and fluidic access to holes drilled through the DMF substrates themselves. As shown in Figure 9, the backing frame contains a fluidic conduit that couples the o-ring face seal around the digital microfluidic substrate through-hole to a CapTite capillary port at the top of the frame.

Although this approach does not offer the same fine control of fluid delivery and removal as the in-plane capillary interface, it provides a convenient method for bulk addition and removal of liquids from the DMF device. The through-hole interface also makes it possible to seal the space between the digital microfluidic substrates with a thin perimeter gasket as shown at right in Figure 9, while still preserving fluidic access to the interior of the device. This approach offers the option of operating the Sandia DMF Hub hermetically sealed, filled with a particular gas mixture (e.g., for cell culture experiments), humidity controlled, pressurized, or even flooded with oil to allow water-in-oil digital microfluidic applications. A variant of the through-hole interface backing frame (not shown) includes a receptacle sized to accept and seal around a 20 µL pipette tip, allowing liquids to be delivered to the fully assembled Hub by either manual or automated pipetting, as well as by capillary interface.

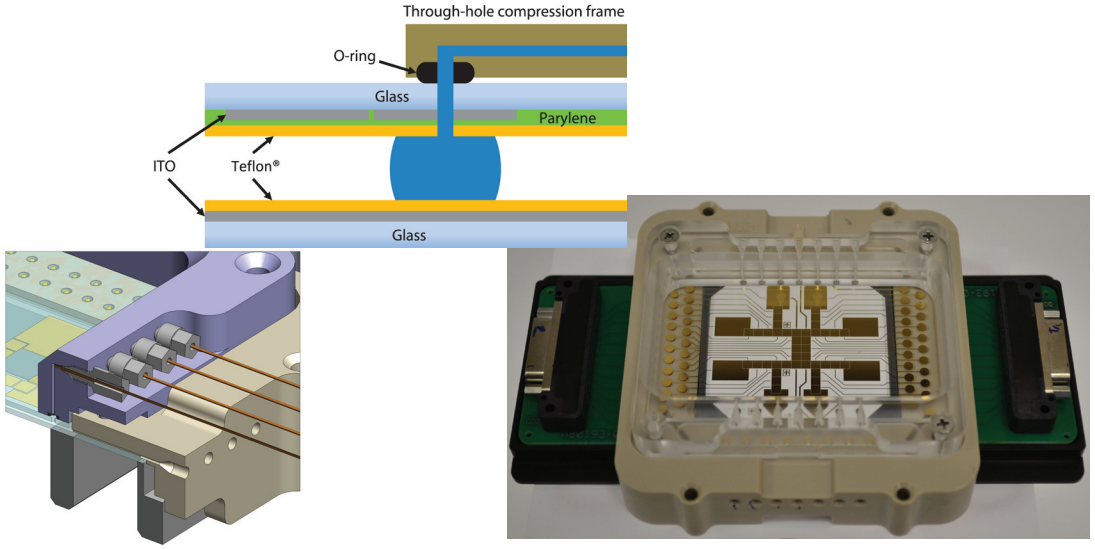


Figure 9: Cross-sectional schematics (top), solid model close-up section view (left) and photograph (right) of the through-hole interface backing frame, an alternative to the in-plane capillary interface for fluid transfer. The image at right also shows the partially assembled digital microfluidic Hub with a silicone perimeter gasket installed between the substrates.

Optical Access

As Figure 5 shows, the manifold frame of the Hub provides an essentially unrestricted field of view of the two digital microfluidic substrates from either side of the Hub. Moreover, the Hub provides enough physical space that short-working-distance, high-numerical-aperture optics can be used for high-magnification visualization of droplet manipulations. Two-sided optical access provides other benefits, particularly when the conductive layer of both digital microfluidic electrode and ground plane substrates consists of transparent indium tin oxide (ITO). In this case, transmission and epifluorescence microscopy can be employed, and analytical techniques like optical absorbance, laser-induced fluorescence, and even Raman spectroscopy can be applied in situ to droplet-bound samples on the DMF device.

Electrode Design, Interface, and Control

Figure 10 shows the arrangement of electrodes, conductive traces, and contact pads for a typical digital microfluidic substrate used as part of the Sandia DMF Hub. Digital microfluidic substrates are fabricated using 50 mm × 75 mm × 1 mm glass slides coated on one side with either transparent, conductive ITO or a conductive metal film such as chrome or gold. Photolithographic patterning and wet chemical etching are used to define digital microfluidic electrodes connected to contact pads arrayed near the short ends of the substrate. Typical digital microfluidic electrode pads are 2.5 mm square, corresponding to a nominal digital

microfluidic droplet volume of roughly 1.2 µL for a manifold frame with a gap spacing of 185 µm. After electrodes are patterned, substrates are coated with a 4 µm conformal layer of vacuum-deposited parylene-C for electrical insulation, then spin-coated with a thin layer of Teflon® AF to render their surfaces hydrophobic. Ground plane substrates are fabricated by simply applying a Teflon AF coating to an unpatterned, ITO-coated glass slide.

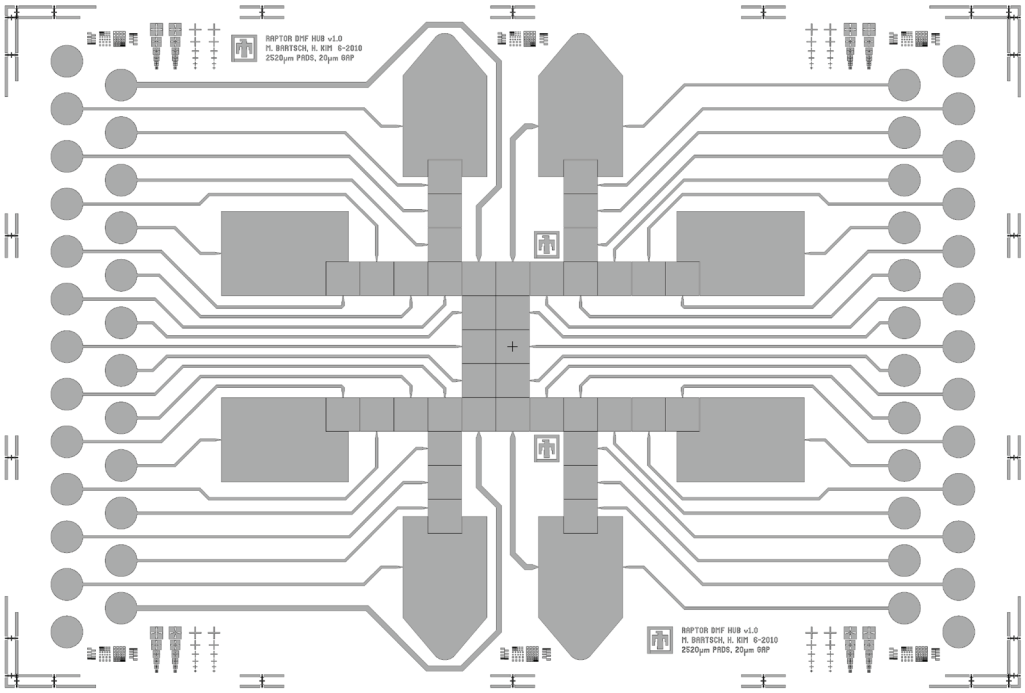


Figure 10: Schematic illustration of the layout of one digital microfluidic electrode substrate design used in the Sandia Digital Microfluidic Hub.

Currently, up to 46 independently addressable connections to the digital microfluidic substrates are made by arrays of spring-loaded pogo pins at the non-overlapping ends of each substrate. Pogo pins are coupled to an off-Hub switching power supply through a pair of circuit boards and compact cable connectors integrated into the manifold frame assembly. The power supply includes a function generator and compact AC high-voltage amplifier to produce typical droplet actuation voltages of 50 V_{rms} to 150 V_{rms} at ~15 kHz. Aromat-style solid-state relays are used to dynamically assign one of three possible voltage states (high, ground, and float) to each of the 46 electrodes on the Sandia DMF Hub.

Voltage switching and digital microfluidic electrode state assignments are communicated to the power supply using custom control software, which includes a graphical user interface (Figure 11) with options for both manual electrode actuations and automation through scripting. A simple scripting

interface provides a small vocabulary of pad actuation primitive operations, allowing even complex sequences of droplet maneuvers to be scheduled and executed effectively. For more advanced laboratory automation tasks, device driver modules provide the ability to control and sequence the actuation of pumps, valves, heaters, and other system components in coordination with droplet actuations on the Sandia DMF Hub.

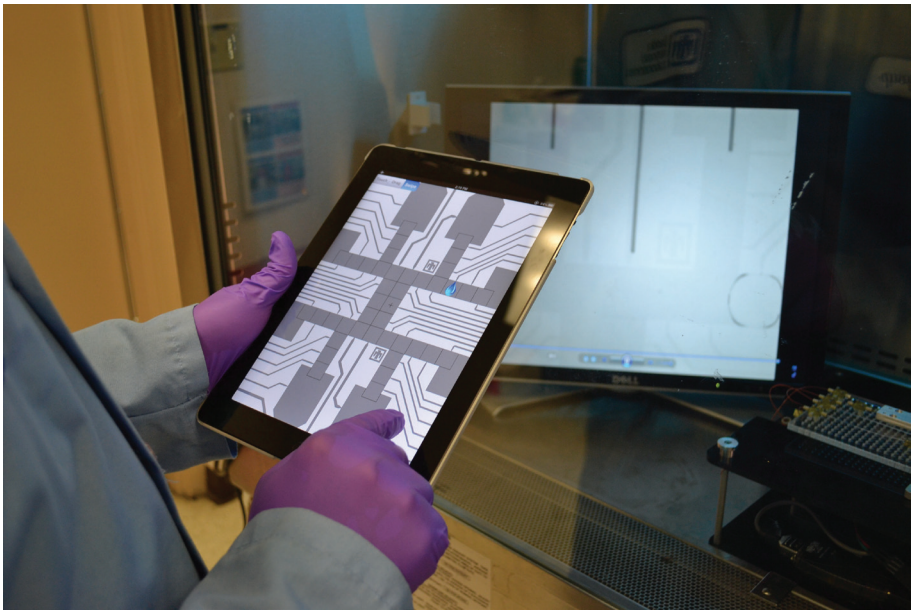


Figure 11: Droplet actuation graphical user interface control software implemented on a tablet PC (iPad) for remote operation of the Sandia DMF Hub.

12. Product Comparison

At present, there is no commercially available equivalent to the Sandia Digital Microfluidic Hub or the open-architecture capability it offers to seamlessly bridge discretized droplet-based microfluidic operations and continuous-flow capillary or lab-on-a-chip fluidics. While companies like Advanced Liquid Logic have produced laboratory instruments featuring digital microfluidic elements, they typically have been implemented as consumable cartridges operating in isolation as part of a predefined and narrowly prescribed protocol inside the “black box” of the instrument, thus entirely inaccessible to the user.

In contrast, the operation of the Sandia DMF Hub is intended to be as transparent, flexible, and accessible as possible to the user, providing the means to effectively and inexpensively integrate commercially available or custom-built fluidic components, instruments, and processing modules to enable the automation and optimization of arbitrarily complex sample preparation protocols. While no direct analog exists in the commercial marketplace, the role filled by the Sandia

DMF Hub most closely parallels pipette-based sample transfers, either performed manually by a laboratory technician or in automated fashion by a pipetting robot. Accordingly, to better compare the benefits offered by the Sandia DMF Hub in context, we return to the specific automated molecular biology example presented above, namely the execution of the Nextera next generation sequencing library preparation process. As the product comparison matrix shows, a number of vendors are now selling integrated systems for performing next generation sequencing library preparation, including robot-based systems by Beckman-Coulter (SPRIworks Fragment Library System I), Caliper (Sciclone NGS Workstation), and IntegenX (Apollo 324). The one next generation sequencing sample preparation system currently available that does not rely on a pipetting robot is the NuGEN Mondrian SP, a digital microfluidic-based system developed in conjunction with Advanced Liquid Logic.

Comparison Matrix

	Company / Manufacturer					
	Generic (H. sapiens)	Sandia	Beckman-Coulter	Caliper	IntegenX	NuGEN
Model Name / System	Manual Nextera™ Protocol	Digital Microfluidic Hub-enabled Nextera AMB	SPRIworks Fragment Library System I	Sciclone NGS	Apollo 324	Mondrian SP
Working Principle	Manual pipetting	Digital microfluidics	Pipetting robot	Pipetting robot	Pipetting robot	Digital microfluidics
List price	$30/hour	$4,000*	$42,000	$180,000	$79,500	$22,500
System Weight / Volume	200 lbs / 12 ft^3	15 lbs / 1.2 ft^3	123 lbs / 7 ft^3	425 lbs / 30 ft^3	214 lbs / 14 ft^3	25 lbs / 1.7 ft^3
Sample Throughput / Run	1	1-4	1-10	8-96	1-32	1-8
Library Fragmentation	N/A	Yes	No	No	No	No
Library Enrichment/PCR	N/A	Yes	No	No	No	No
Size selection	N/A	Yes	Yes	Yes	Yes	No
Input DNA**	50 ng	5 ng	3000 ng to 5000 ng	3000 ng	200 ng to 1000 ng	100 ng
End-to-End Run Time**	4 hr	2 hr	5 hr + 2 hr (Fragment/PCR)	5 hr + 2 hr (Fragment/PCR)	4 hr + 2 hr (Fragment/PCR)	6 hr
Minimum Volume	0.1 µL	0.1 µL	1 µL	0.5 µL	5 µL	0.3 µL

*Assuming high volume production quantities
**With next generation sequencing library preparation assays validated on the specific platforms

Improvements upon competitive products

From the standpoint of integrating disparate laboratory instruments, subsystems, and operations into a unified workflow, the closest approximation to the functionality provided by the Sandia DMF Hub is offered either by a laboratory technician transferring samples from one station to the next by manual pipetting or by an expensive pipetting robot performing much the same function in much the same way. In either case, such a laboratory workflow can incorporate only unit

operations that are both amenable to pipette transfer and accessible to the robot or technician.

Pipette-based approaches can deliver volumes as small as 100 nL, but become increasingly imprecise as working volumes drop below about 10 µL. Pipetting accuracy and precision can also be compromised by fluids with different viscosity or surface tension characteristics, further complicating operations with very small volumes. Additionally, the comparatively "open" format required for top-down pipette-based automated liquid handling (e.g., 96-well plates) provides opportunities for evaporation and contamination while fundamentally limiting the kind of fluidic operations that can be performed on samples. Moreover, robotic pipetting systems for laboratory automation tend to be very expensive, making them impractical for use in smaller facilities without dedicated, high-throughput sample-processing workflows.

The Sandia DMF Hub eliminates the need to compromise on either performance or cost effectiveness in the interest of pipette-compatibility when assembling laboratory automation solutions.

In the world of pipette-dominated laboratory automation, all sample processing tools must conform to the interface requirements and volume limitations of the pipetting robot. The fact that the Sandia DMF Hub imposes no such restrictions means that virtually any kind of sample processing device can be effectively adapted to operate in a digital microfluidic-enabled automation workflow. Not only does this paradigm allow automation systems built around a central digital microfluidic hub to utilize a broader cross-section of commercially available elements in assembling modular subsystems, it also provides extraordinary flexibility in designing and optimizing custom modules tailored to perform specific sample preparation operations. As a result, the open architecture and near-universal interface capabilities offered by the Sandia DMF Hub eliminate the need to compromise on either performance or cost effectiveness in the interest of pipette-compatibility when assembling laboratory automation solutions.

Therefore, the Sandia DMF Hub represents a truly unprecedented reinvention of small-scale liquid handling and sample processing technology. As such, there simply is no directly comparable or competitive technology currently available that offers the same level of connectivity, flexibility, and sample-efficiency.

Limitations and criticisms

The Sandia Digital Microfluidic Hub itself is not a standalone turnkey instrument, and therefore does not present, on its own, an apples-to-apples comparison to the kind of purpose-built instruments described above in the product comparison

matrix list of "competitors." Nevertheless, as the Nextera library prep example illustrates, the flexibility of the Sandia Hub provides a wealth of cost-effective options and opportunities for implementing small- to intermediate-scale laboratory workflow automation solutions. In this sense, the primary limitation of the Sandia DMF Hub — its reliance on supplemental hardware to address specific applications — is also its greatest strength. Instead of a large, expensive system tailored to a very specific application, the Sandia DMF Hub provides a compact, flexible means to coordinate and integrate the functionality of a number of individually optimized, application-appropriate, modular subsystems.

Competitors might observe that the reusable substrate paradigm of the Sandia Hub poses risk of run-to-run sample carry-over that could be avoided in a disposable format. This is not a fundamental limitation of our technology, but rather reflects a decision to emphasize operational flexibility while incorporating robust decontamination strategies to prevent cross-contamination. Competitors might also note the relatively high cost of the reusable Sandia digital microfluidic substrates. As suggested above, these costs reflect the limitations of our current in-house fabrication processes, and would be substantially reduced in mass production. Even at the current substrate price point, however, the reduced consumption of expensive enzymatic reagents due to the very small sample volumes required by the Sandia DMF Hub (one-tenth the typical volume for pipette-based systems) could quickly offset the cost of the digital microfluidic substrates.

13. Product Use

Principal applications

The advent of next generation DNA sequencing technology has yielded a quantum leap in the field of genetic analysis — what once required a decade-long, multibillion dollar Human Genome Project can now be reproduced in 1-2 weeks for less than $5,000. Despite advances in these sequencing technologies, upstream library (sample) preparation protocols, which require numerous sample processing steps and hours of hands-on laboratory time, have not benefitted from comparable increases in speed or efficiency. While automation of the library preparation process can help overcome this widely recognized bottleneck, current approaches rely on large and expensive pipetting robots designed for use in dedicated high-throughput sequencing facilities. To fully realize the promise of next generation sequencing for more ubiquitous, individualized, decentralized applications (e.g., personalized genomic medicine, point-of-care diagnostics, and public health screening), technologies automating next generation sequencing sample preparation must also become more affordable and accessible. The Sandia Digital Microfluidic Hub was

designed specifically to address the laboratory automation and sample preparation needs of just such small and medium-sized facilities and applications.

As indicated in the product comparison matrix, the Nextera automated molecular biology prototype system exemplifies the practical benefits offered by the Sandia DMF Hub for integrating and automating realistic sample preparation workflows generally, and workflows relevant to next generation sequencing in particular. The estimated cost of the Nextera automated molecular biology system is less than one-fifth that of its closest competitor and is at least an order of magnitude less expensive than any robot-based system currently available on the market. Moreover, the least expensive commercially available system, the NuGen Mondrian SP, does not perform key next generation sequencing library construction steps, such as DNA fragmentation, library enrichment by PCR, or size-based target selection.

We expect the future Sandia DMF Hub-based automation solutions will pave the way for a new era of personalized genomics.

As a direct result of the unique flexibility and connectivity of the Sandia DMF Hub, our sample Nextera automated molecular biology implementation is the only system to date that can execute the full end-to-end library construction process including all key steps, as summarized in the product comparison matrix. Fully automated with in situ library validation and integrated to personalized sequencers (Illumina MiSeq or Life Technologies' Personal Genome Machine), we expect that future Sandia DMF Hub-based automation solutions will pave the way for a new era of personalized genomics.

Moreover, using the Sandia system, the entire Nextera library preparation process takes only 2 hours to complete — less than half the time of the next fastest competing system. The sample volume efficiency benefits of the Sandia DMF Hub also mean that the Nextera automated molecular biology system requires only one-tenth the sample and reagent volumes required by the commercially available systems. The Sandia Nextera system also requires only 5 nanograms of input DNA versus the 50 to 5000 nanograms required by competing approaches, including manual bench-top processing. This increased efficiency is especially beneficial in sample-constrained applications like criminal forensics or environmental sampling and in clinical applications where obtaining smaller samples is less invasive to the patient.

Other applications

While molecular biology, and specifically library preparation for next generation sequencing, was the initial application targeted for the Sandia Digital Microfluidic Hub, its flexible interface capabilities and unique design features make it well suited to a range of other applications.

Forensic DNA Fingerprinting

The U.S. Army is currently funding the development of a portable, automated DNA sample preparation and genotyping system for in-theater criminal investigation and intelligence gathering applications. The left image of Figure 12 shows how a system based on the compact DMF Hub can be packaged in a portable form factor for use in the field.

- The Sandia DMF Hub provides the unifying interface between individually optimized DNA extraction, quantitation, PCR amplification, and electrophoretic separation modules.
- The ability to manipulate and utilize very small samples allows the DMF Hub-based system to effectively exploit trace forensic samples.
- The complex genotyping protocol can be executed as a single-button, sample-to-answer procedure requiring no hands-on user involvement beyond the initial introduction of the forensic sample.

Global Biosurveillance

The low-cost, low-power operation, automation capabilities, and compact form factor of the Sandia DMF Hub make it well suited to process infectious samples in remote, low-resource locations, facilitating efforts to identify and interdict disease outbreaks at their source before they become widespread.

- The DMF Hub can enable automated manipulation, neutralization, pre-screening, and packaging of infectious samples to enable early identification of emerging pathogens in remote locations.
- In a closed and fully automated workflow, infectious clinical samples are rendered non-infectious and pathogen RNA/DNA are extracted and stabilized for transport to centralized facilities for analysis and identification.
- The small size and automation capabilities of the DMF Hub also enable its use in processing highly infectious samples in laboratory biosafety enclosures at high-resource centralized facilities (e.g., Centers for Disease Control).

Automated Cell Culture

The droplet manipulation capabilities and interface options offered by the Sandia DMF Hub provide a unique option for automating the repetitive and labor-intensive manual procedures typical of cell culture maintenance, as shown in the right image of Figure 12.

- Adherent cells can be cultured in situ on the DMF device, while droplets containing fresh media are brought to them.
- Droplets containing cells in suspension can be readily moved, split, merged,

and mixed with cell-free droplets to maintain culture viability.

- The fluidic interface of the DMF Hub provides options for dosing cells in place for pharmacological studies, viral transduction, or tagging with fluorescent markers.
- Using the through-hole interface and a perimeter gasket, the DMF Hub can expose cultured cells to controlled humidity or gas mixture environments.
- Two-sided optical access enables in situ fluorescence microscopy of cultured cells or controlled illumination for studying photosynthetic organisms.

Figure 12: (Left) Sandia DMF Hub-based system packaged for deployment in the field. (Right) DMF Hub for automated cell culture processing in a biosafety containment hood. The embedded graph shows the high cell viability cultured on the DMF hub. The remote operation through a handheld GUI interface provides safe but real-time experimental control of potentially infectious or hazardous samples.

R&D Tool

By reducing the barrier to entry and making digital microfluidic technology readily accessible to a wide cross-section of potential users, the Sandia DMF Hub could catalyze innovation and complete the transformation of digital microfluidics from laboratory curiosity to mainstream technology.

- Its low-cost, robust operation, and plug-and-play capabilities make the Sandia DMF Hub ideal as a “discovery platform” or digital microfluidic “developer’s kit” for amateurs and professionals alike.
- A basic discovery kit including a Hub, power supply, software, and DMF substrates would enable even non-technical users to perform simple droplet manipulations.
- Advanced users could leverage the connectivity of the DMF Hub to perform complex experiments, develop DMF-enabled product prototypes, or implement small-scale do-it-yourself laboratory automation solutions.

14. Summary

Molecular biology provides the crucial tools and techniques that have enabled the current revolution in biotechnology, bioinformatics, and genomics. Rapid growth in these fields, combined with the advent of demanding high-throughput and next generation sequencing techniques in particular, have motivated an industry-wide effort to streamline and automate the often time- and labor-intensive molecular biology sample preparation protocols, which increasingly represent the critical bottleneck in these workflows. The Sandia Digital Microfluidic Hub overcomes this bottleneck by functioning as a sample distribution nexus that enables the interconnection of diverse processing and analysis modules to automate complex microliter-scale molecular biology sample-preparation protocols.

The Sandia Digital Microfluidic Hub represents an entirely new automation paradigm and enabling technology.

In many ways, current molecular biology laboratory practices resemble an office in which all data is transferred by someone with a USB flash drive walking from computer to printer to fax machine and back. By analogy, current pipette-based laboratory automation approaches amount to buying an expensive robot to do the walking. In the context of our notional laboratory automation workplace, the Sandia Digital Microfluidic Hub is the inexpensive network router that enables all the office productivity tools to interact and communicate seamlessly via office intranet — without the robot and all the walking.

What technology benefits will it provide?

- The Sandia Digital Microfluidic Hub represents an entirely new automation paradigm and enabling technology. The advanced connectivity, operational flexibility, and small-volume sample manipulation capabilities of the Sandia DMF Hub constitute a compelling alternative to the “tyranny of the pipette” for molecular biology automation.
- The small form factor of the DMF Hub makes it practical for use in distributed and field-deployable applications such as global biosurveillance, expeditionary forensics, and point-of-care diagnostics, where small size, portability, scale-appropriate sampling, and reduced cost are paramount.
- The open architecture, robust operation, low cost, and plug-and-play simplicity of the Sandia Digital Microfluidic Hub make it ideal as a “developer’s kit” for prototyping and evaluating custom automation systems tailored to address specific problems in the life sciences.
- The unprecedented connectivity options offered by the Sandia Digital Microfluidic Hub represent a revolutionary reimagining of what digital

microfluidic technology itself can accomplish — a fulfillment of its promise and a transcendence of its longstanding limitations.

What financial benefits will it provide?

Because the Sandia DMF Hub can effectively manipulate sample and reagent volumes at scales at least an order of magnitude smaller than those required for pipette-based operations, systems incorporating the DMF Hub can dramatically reduce assay costs due to the consumption of expensive reagents.

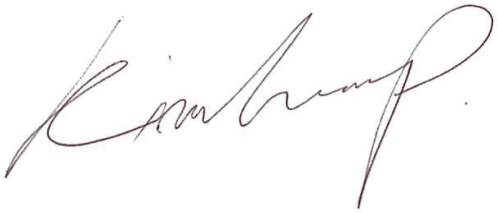
- Because it operates entirely at the microliter scale, our DMF Hub-enabled automated molecular biology system can perform the full, end-to-end Nextera NGS library construction protocol in less than 2 hours, dramatically reducing the cost of sequencing-based research and diagnostics.
- The Nextera library preparation example further illustrates how the low cost, unique connectivity, and modularity of the Sandia Digital Microfluidic Hub make it possible to construct fully integrated, cost-competitive laboratory automation systems by leveraging inexpensive, commercially available components.
- The open architecture, robustness, and modularity of the Sandia DMF Hub uniquely position it to serve as a common framework or "universal" standard for sample preparation and microliter-scale fluid manipulation. Widespread adoption of the DMF Hub would dramatically reduce the time and expense of implementing and integrating new laboratory automation systems and protocols relevant to molecular biology and other small scale applications.

Wow! Factor

The Sandia DMF Hub effectively replicates and improves upon the sample manipulation functionality of a pipetting robot in a laboratory automation workflow, but at a fraction of the size, cost, and complexity. The universal interface and modular integration capabilities of the DMF Hub uniquely enable the kind of innovative, efficient, and economical "sample-in, answer-out" automation solutions needed to make the revolutionary vision of ubiquitous, personalized genomic medicine a reality.

15. Affirmation

By submitting this entry to R&D Magazine I affirm that all information submitted as a part of, or supplemental to, this entry is a fair and accurate representation of this product.



Hanyoup Kim

APPENDICES

Appendix A: Submitter Information

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Appendix C: Patents

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
61/478,641	04/25/2011		220	SD-11945PRO		

CONFIRMATION NO. 8169

21496
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FILING RECEIPT

OC000000047718309

Date Mailed: 05/20/2011

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

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Kamiesh D. Patel, Dublin, CA;
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Power of Attorney:
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If Required, Foreign Filing License Granted: 05/17/2011
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 61/478,641**
Projected Publication Date: None, application is not eligible for pre-grant publication
Non-Publication Request: No
Early Publication Request: No
Title

DIGITAL MICROFLUIDIC PLATFORM AND METHOD FOR INTERFACE

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international

Appendix C: Patents (cont.)

DIGITAL MICROFLUIDIC PLATFORM AND METHOD FOR INTERFACE

STATEMENT OF GOVERNMENT INTEREST

[001] This invention was made with Government support under Government Contract No. DE-AC04-94AL85000 awarded by the U.S. Department of Energy to Sandia Corporation. The Government has certain rights in the invention, including a paid-up license and the right, in limited circumstances, to require the owner of any patent issuing in this invention to license others on reasonable terms.

DESCRIPTION OF THE PROBLEM

[002] Digital microfluidics (DMF) is a technology in which a substrate patterned with electrodes and coated with dielectric insulator and a hydrophobic film may be used to manipulate droplets. Potential DMF applications are numerous and include biological assays, chemical reaction engineering, medical diagnostics, particle synthesis, separations, lab automation, sample preparation, and particle forensics. The practical challenges of implementing DMF technology, however, presently limit the scope of its applications.

[003] DMF technology, also sometimes referred to as droplet microfluidics or electro-wetting on dielectric (EWOD), is typically implemented in two distinct formats: open and closed. In open format DMF, droplets move atop a single electrode-patterned substrate (**FIG. 1A**), while in closed format DMF, droplets are partially confined between two substrates (**FIG. 1B**).

[004] In open format operation, grounded traces patterned on the electrode substrate allow droplet motion when actuation voltages are applied to individually addressed electrode pads. Open format DMF imposes limitations on the kind of droplet moving geometries that can be employed due to the need to always route both ground and actuation traces in close proximity on the same DMF substrate. Overall, droplet actuation on an open format devices is somewhat more difficult to achieve consistently because electric field gradients and transients are confined to a relatively small region at the base of the droplet in

Appendix C: Patents (cont.)

For: DIGITAL MICROFLUIDIC PLATFORM
AND METHOD FOR INTERFACE
In re. BARTSCH, et al.
Attorney Docket Number SD-11945 PRO

1/8

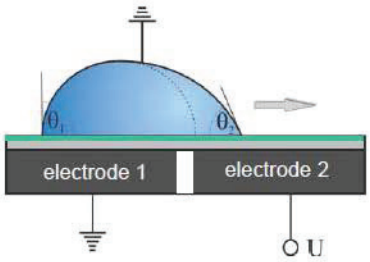

FIG. 1A

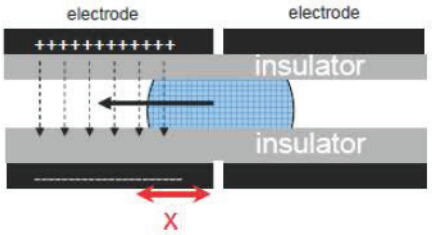

FIG. 1B

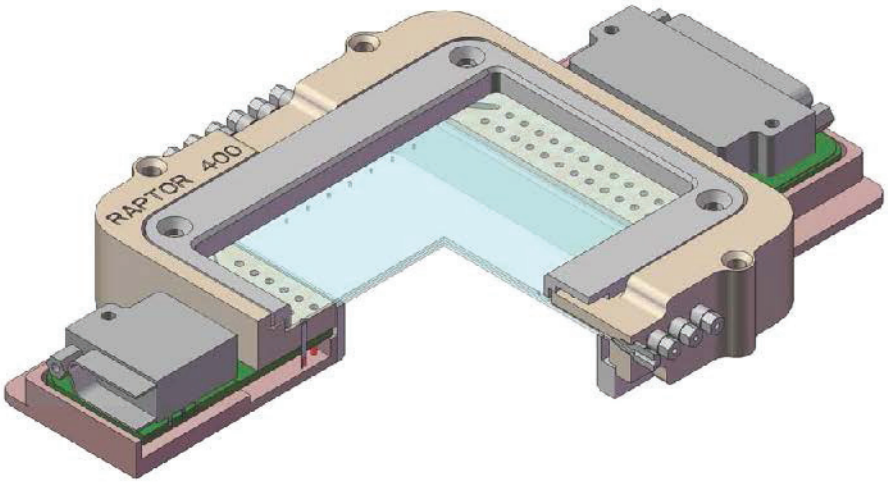

FIG. 3

Appendix D: Letters of Support

CENTER FOR INFECTION AND IMMUNITY
the path forward

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January 26, 2012

Kamlesh D. Patel, Ph.D
Senior Member of the Technical Staff
Biosystems Research Group, Sandia National Laboratories
MS 9292, PO Box 969
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Livermore, CA 94551-0969

Dear Kamlesh (Ken) Patel

On behalf of Dr. Ian Lipkin, myself, and Center of Infection and Immunity (CII) at the Mailman School of Public Health at Columbia University, we are very enthusiastic and excited about the Automated Molecular Biology Digital Hub platform being developed by your team at Sandia National Laboratories. We believe that this technology will increase the rate of detection of pathogens in diagnostics and biosurveillance. Furthermore, your Hub can be used in field-based assay systems that employ state-of-the-art analysis, addressing a critical gap in our area of work. This will allow us to execute assays closer to the source of sample collection generating information from nucleic acids before they degrade.

The digital hub will be an essential component to implementation of our staged strategy for rapid pathogen detection. The CII has been engaged in infectious disease diagnostics and pathogen discovery for more than 25 years. It is presently the largest laboratory focused in this research and service area and is the only academic center recognized for such work by the Pan American and World Health Organization (PAHO/WHO Collaborating Centre for Diagnostics in Zoonotic and Emerging Infectious Diseases. CII annually receives more than 12,000 uncharacterized clinical samples from humans, domestic animals and wildlife collected in Africa, Asia, Europe, North and South America, and Oceania through collaborative research projects with the Bill and Melinda Gates Foundation, DoD, Google.org, National Institutes of Health, and as a service to the CDC, Medical Research Councils of the Australia and the UK, WHO, Wildlife Conservation Society, USDA, and more than 50 laboratories worldwide. We understand too well the complexity and issues with developing new technologies and applications and strive to establish long term collaborations with the leading scientists and organizations. We fully support your efforts to develop this component and recognize the innovative potential and impact this technology. Being able to circumvent this shipping with stable nucleic acid processed in the field would be a key win in global biosurveillance initiatives.

Sincerely,

David L Hirschberg

Appendix D: Letters of Support (cont.)

Department of Chemistry
UNIVERSITY OF TORONTO http://www.chem.utoronto.ca
Lash Miller Chemical Laboratories 80 St. George Street Toronto, Ontario M5S 3H6

January 26, 2012

RE: Nomination for an R&D100 Award

Dear Committee:

My name is Aaron Wheeler; I am an Associate Professor in the Chemistry and Biomedical Engineering Departments at the University of Toronto. I am an expert in the area of microfluidic electromechanical droplet manipulation, known popularly as "digital microfluidics." I have published more than 50 papers and have filed 9 patents on various aspects and applications of digital microfluidics (many of which can be found at microfluidics.utoronto.ca), making me (arguably) the top academic scientist in this area in the past few years. I write this not to brag, but to make the case that my opinion in this area is one worth considering.

I recently became aware of the Automated Molecular Biology platform being developed by Sandia National Laboratories. This platform is built around an ingenious idea -- a low-sample/reagent-volume digital microfluidic "hub" that connects analytical and processing modules through in-plane capillary connections. The value of this approach is the modularity that it will bring to complex multistep protocols without sacrificing analyte concentration losses (i.e., analytes do not suffer from dilution as they would in nearly any alternative approach for linking several preparation/analysis steps). The modularity of this system will allow Sandia to develop automated solutions to a host of different problems, without requiring a complete re-design for each new application that is tackled. I am convinced that this innovation represents a game-changer in the area of automated analytical systems.

In summary, I give my highest recommendation for this invention for your consideration. Please feel free to contact me with any questions.

Sincerely,

Aaron Wheeler

AssociateProfessor of Chemistry
Canada Research Chair in Bioanalytical Chemistry
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Appendix E: Article

SANDIA LAB NEWS • April 22, 2011 • Page 3

Technology aims to rapidly identify and characterize unknown pathogens

At the heart of RapTOR a microfluidic 'Grand Central Station'

Story by Patti Koning • Photos by Dino Vournas

TINY BUT GRAND — Ken Patel works on the digital microfluidic hub, the "Grand Central Station" of RapTOR that manages and routes samples. He won the Society for Laboratory Automation and Screening's $10,000 Innovation Award for this work.

More often than not, you can't put a price tag on the rewards of scientific research — satisfaction at solving a tough problem, the respect of peers, knowing your work will have a larger impact on the world. But sometimes you can: just ask Kamlesh (Ken) Patel (8621). He recently won the Society for Laboratory Automation and Screening (SLAS) $10,000 Innovation Award for his outstanding podium presentation, "Preparation of Nucleic Acid Libraries for Ultra-High-Throughput Sequencing with a Digital Microfluidic Hub."

"The SLAS Innovation Award was created specifically to recognize cutting-edge research and the individual behind the work, and Kamlesh's exploration into nucleic acid libraries for ultra-high-throughput sequencing with a digital microfluidic hub will impact the scientific community for years to come," says SLAS Innovation Award Committee Chair Jörg Kutter.

Sandia CaliforniaNews

While Ken's name is on the award, he's quick to point out that his work is part of a much larger effort with contributions from a multidisciplinary team. Led by principal investigator Todd Lane (8623), the RapTOR (Rapid Threat Organism Recognition) Grand Challenge, part of the International, Homeland and Nuclear Security strategic management unit, has the ambitious goal of rapidly identifying and characterizing unknown pathogens. (*Lab News*, Aug. 26, 2010). In an outbreak scenario, whether the result of bioterrorism or a fast-moving, deadly virus like Ebola, RapTOR could greatly accelerate the response. Until you know what's making people sick, treatment is like throwing darts.

Leveraging DNA sequencing technology

Using the latest in DNA sequencing technology, RapTOR aims to transform slow, labor-intensive benchtop sample preparation methods to an automated microfluidic platform to create a fast, efficient, and flexible tool. "We're taking advantage of DNA sequencing technology," Ken says. "Reading the genetic code, the original building blocks, allows you to begin characterizing a pathogen at the most basic level."

But getting at those building blocks is not easy — clinical samples are packed with information, most of which is not of use in characterizing an unknown pathogen. For example, more than 99 percent of the DNA in a blood sample is the human genome. DNA in a nasal swab is 90 percent human-derived and much of the rest is garden-variety bacteria. Suppressing all that background DNA is essential to get at the unknown pathogen.

DNA sequencing technology has evolved at a tremendous pace, even surpassing Moore's Law, the 45-year-old prediction that computer processing power would double every two years. The pre-sequencing steps, however, have hardly changed since the bacteriophage genome was first sequenced in the mid-1970s.

Ken leads the Automated Molecular Biology (AMB) research to both scale down and automate traditional sample preparation methods such as normalization, ligation, digestion, and size-based separation — methods that traditionally require a skilled scientist and take days or even weeks. A critical component of RapTOR is bringing together the different sample prep steps to create a "one-stop shop" that connects to a DNA sequencer. Key to this is the digital microfluidic hub.

The hub is a Grand Central Station for samples, routing them from one step to the next with the flexibility to skip or repeat steps on the fly. But imagine a train station in which some trains are orders of magnitude larger than the others, and some travel at the speed of light and others at 60 mph. The digital microfluidic hub is designed to negotiate these differences, functioning like a train station that can shrink and enlarge trains as necessary and manipulate their speeds.

Instead of trains, droplets are the mode of transportation in this station and voltage serves as the engine. The sample is cargoed within a microliter-scale droplet that is spatially moved across the Teflon-coated surface of the hub when electrostatic forces are appropriately applied. The hub also manages the size of the sample, extracting the right amount for each process.

Reagents dispensed as needed

Size is only one variable that the microfluidic hub manages. Reagents and enzymes necessary for different manipulations are stored in reservoirs connected to the hub and dispensed as needed. "If we need to do a reaction at a set temperature, we can move the sample through a connector tube off the hub into a heated microreactor, perform the reaction at temperature with appropriate reagents, and then redispense the sample back onto the hub for the next processing step," Ken says. "This is where AMB becomes very powerful — it allows you to connect multiple, different components together through a common flexible interface. All of the microreactors are replaceable, so contamination is not an issue."

KEN PATEL and Numrin Thaitrong (8621) examine the digital microfluidic hub.

At the start of the Grand Challenge, the AMB team wasn't sure how efficiently they could repeatedly move droplets on and off the hub. Turns out, the ability to move the droplets is one of the most powerful features of the device.

"We've concluded that this is one of the main contributions we've made to the field," Ken says. "Interfacing to a droplet and other microfluidic chips is not just possible, it's quite effective and a good path forward for processing samples."

As the AMB team continues to refine the digital microfluidic hub, they are also working on a parallel project to culture cells within the droplets. "There are several exciting advantages to this approach — we can work with different microcultures of cells independently on the device. It is possible to study infections at the cellular level, working with small amounts of cells — thousands at best, not millions — in a hermitically sealed, safe environment," Ken says. "The end goal is a device that could be used in Biosafety Level-3 containment, enabling safe diagnosis and research of infectious agents."

Expanding the role of this technology, Ken was recently awarded additional funding from the US Army Criminal Investigations Laboratory to develop a microfluidic-based approach for genotyping in the field. Such a device would allow law enforcement to rapidly process forensic evidence at the crime scene for matching DNA, rather than sending a sample to the lab and waiting days for confirmation, generating immediate intelligence that can then be applied to the unfolding situation.

The digital microfluidic hub could have a wide range of applications — from crime scene investigators to first responders to a general practitioner's office.

"An eventual goal might be to develop an all-in-one portable device, a sequencer with a sample prep front end. We have portable sensors, so why do not DNA sequencing in the field?" says Ken.

"Going to the DNA level gives you so much definitive information, amazing characterization capabilities that we just don't have today. It's the new revolution, a really interesting and exciting way of doing research and solving clinical problems. It just makes sense for Sandia to be on that leading edge, applying this research to our national security missions in biodefense."

HANYOUP KIM (8621) checks out the Rapid Threat Organism Recognition (RapTOR) device prototype. The digital microfluidic hub, visible inside the case, serves as the "Grand Central Station" of the device, routing and managing samples for speedy identification and characterization.

Appendix F: Media Coverage

slas SOCIETY FOR LABORATORY AUTOMATION AND SCREENING
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For Immediate Dissemination:
February 3, 2011

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SLAS Selects $10,000 Innovation Award Winner

LabAutomation2011 Awards Program Highlights the Latest Laboratory Automation Advances

CHICAGO – The Society for Laboratory Automation and Screening (SLAS) is pleased to announce the winner of the $10,000 SLAS Innovation Award presented at LabAutomation2011. Kamlesh Patel, Senior Scientist, Sandia National Laboratories, was honored for his outstanding podium presentation, *Preparation of Nucleic Acid Libraries for Ultra High Throughput Sequencing with a Digital Microfluidic Hub*.

The winner was announced during the closing plenary session at LabAutomation2011, the world's leading conference and exhibition on emerging laboratory technologies. The conference, held January 29-February 2, 2011 at the Palm Springs Convention Center, Palm Springs, CA, USA, hosted more than 4,400 participants from around the globe.

The SLAS Innovation Award recognizes the top 10 finalists from a roster of submitted abstracts thoroughly reviewed by the Innovation Award Committee. Qualifying abstracts are selected based on their demonstration of extraordinary vision, originality, seminal technology, applications and strategies. Once on-site in Palm Springs, the judging panel attends and evaluates each finalist's presentation and collectively selects the winner of the SLAS Innovation Award based upon the impact on laboratory automation, originality/creativity, quality of the science and oral presentation. The winner is presented with a $10,000 check.

"We are thrilled with the diversity and quality of all submissions for the highly competitive SLAS Innovation Award," says SLAS Innovation Award Committee Chair Jörg Kutter, Ph.D. "All top 10 presentations were extraordinary, but the solid presentation by Kamlesh clearly won the coveted award. The SLAS Innovation Award was created specifically to recognize cutting-edge research and the individual behind the work, and Kamlesh's exploration into nucleic acid libraries for ultra high throughput sequencing with a digital microfluidic hub will impact the scientific community for years to come."

In addition to the $10,000 SLAS Innovation Award, SLAS annually awards the SLAS New Product Award (NPA) designation to up to three of the top new products showcased on the LabAutomation exhibit floor. This year's NPA winners are:

- Cellasic – Pearl Microfluidic Hepatocyte Culture System
- Covaris, Inc. – LE220 Ultrasonicator
- Microsaic Systems Ltd – Microsaic 3500 MiD

-more-

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The Society for Laboratory Automation and Screening (SLAS) is a new non-profit scientific organization uniting the Society for Biomolecular Sciences (SBS) and the Association for Laboratory Automation (ALA). The SLAS mission is to be the preeminent global organization providing forums for education and information exchange to encourage the study of, and improve the science and practice of, laboratory automation and screening.

Society for Biomolecular Sciences SBS ALA Association for Laboratory Automation
Visit SLAS.org

Appendix F: Media Coverage (cont.)

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LabAutomation2011 Awards
Page 2

Each year, SLAS also recognizes the authors of a scientific manuscript published in the Journal of Laboratory Automation (JALA) with the JALA Readers' Choice Award. This year's winning manuscript, authored by scientists from South Korea, is "Development of an Improved Scheduling Algorithm for Lab Test Operations on a Small-Size Bio Robot Platform" (from JALA 15.1 February 2010). The authors include Seung Hoon Shin, Byung June Choi, Sung Moo Ryew, Jung Woo Kim, Dae Shick Kim, Wan Kyun Chung, Hyouk Ryeol Choi and Ja Choon Koo.

Rounding out the awards recipients at LabAutomation2011 are the student poster award winners. SLAS selected a limited number of student posters to be presented at the conference and considered for the Student Poster Awards Competition, which results in cash prizes. LabAutomation2011 student poster award winners are:

- 1st Place – Kelly Karns, University of California, Berkeley
  "Human Tear Fluid-Based Point-of-Care Diagnostics Enabled by Integrated Microfluidic Systems"
- 2nd Place – Amy Hsiao, University of Michigan, Ann Arbor
  "High-Throughput 3D Spheroid Culture and Drug Testing Using a 384 Hanging Drop Array"
- 3rd Place – Vinay J. Nagaraj, The Biodesign Institute at Arizona State University, Tempe
  "Miniature Electronic Biosensor for the Detection of Glycan Biomarkers"

Industry professionals are already looking forward to SLAS2012, the inaugural SLAS Conference and Exhibition which joins former premier events, LabAutomation and the SBS Conference and Exhibition. Peter G. Schultz, Ph.D., Scripps Family Chair Professor in the Department of Chemistry at The Scripps Research Institute will headline the prestigious SLAS2012 line-up as the first in a series of keynote speakers.

For more information on LabAutomation2011, visit http://www.slas.org/LA11, or for more information on SLAS2012, visit http://www.slas2012.org.

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SLAS2012*, February 4-8, 2012, San Diego Convention Center, San Diego, CA, USA is a five-day event bringing together laboratory automation and screening technology scientists, academicians, business leaders and students from around the globe.*

SLAS thanks Agilent Technologies for their Premier Sponsorship contribution to LabAutomation2011, and for their continued commitment to SLAS.

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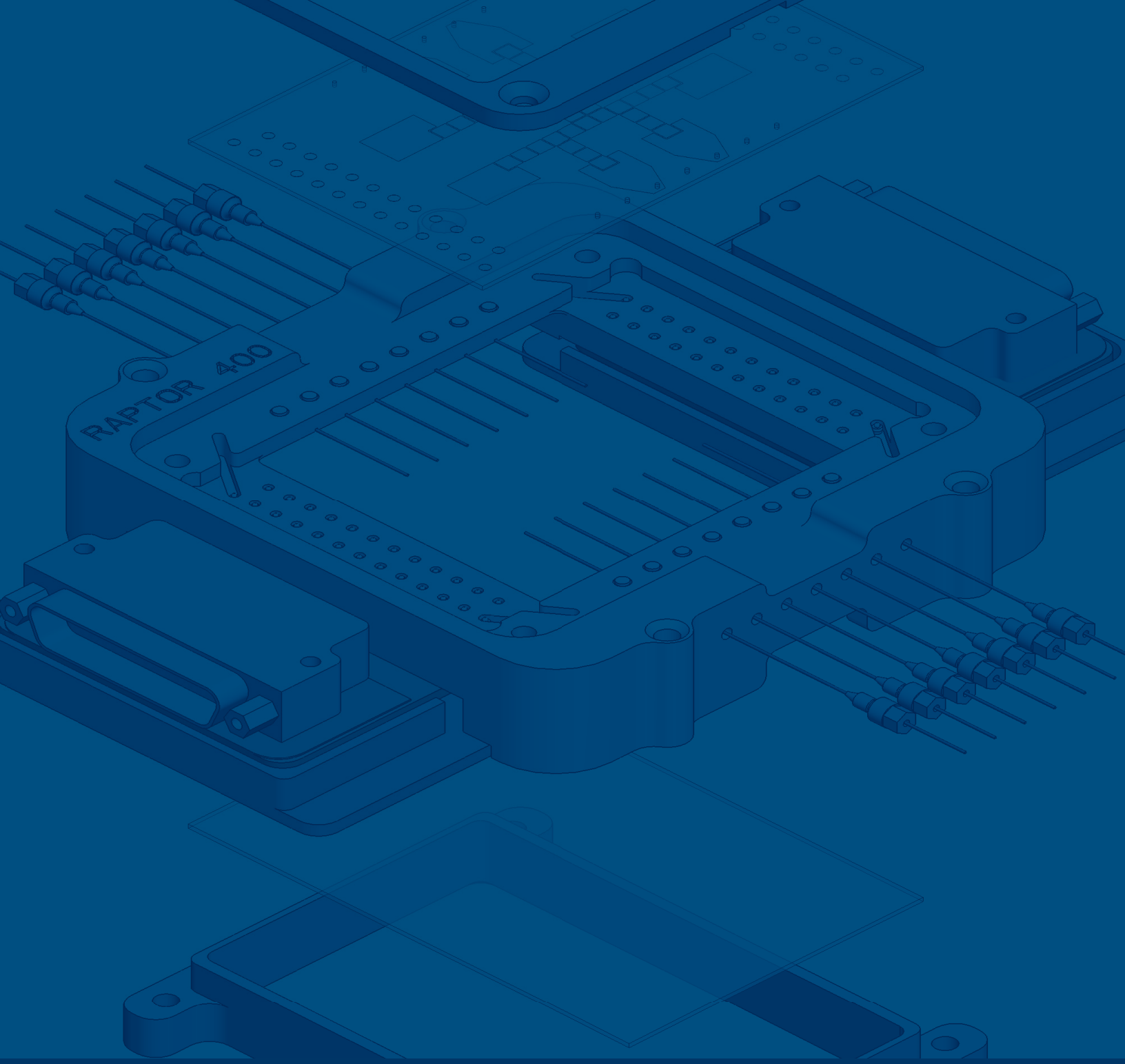

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