

NANO TO NEXT GEN: AUTOMATION GETS PERSONAL

Lab automation – it isn't just for Big Pharma anymore. Providers have developed a range of personal instruments to bring the benefits of automation to the masses. At the same time, new equipment and protocols are enabling the standardization and optimization of such traditionally overlooked areas as cell culture. This article surveys major manufacturers to find out what's new in life science robotics and automation. **By Jeffrey M. Perkel**

One emerging industry trend, according to Douglas Gurevitch, senior development engineer at the **University of California, San Diego**, and executive editor of the *Journal of the Association for Laboratory Automation*, is the move toward reliable nanoliter dispensing.

“Ultrasmall-volume liquid transfer has had a resurgence,” Gurevitch says. Microfluidic lab-on-a-chip systems work at the nanoscale, but their interfaces – not to mention traditional high throughput screening robotics – have tended to operate at the microliter level, meaning researchers still must make more material than they need, and generate more waste.

“Now there's new technology out there that allows you to work at a smaller scale,” he says.

One such system is **TTP LabTech's** mosquito. Commercial director Jas Sanghera says the company had two primary considerations in developing the mosquito: maintaining the accuracy and reliability of microliter-dispensing systems, and avoiding cross-contamination.

The second aim may be accomplished either by washing reusable components or using disposable pipettes. However, since washing becomes less efficient as volumes get smaller and concentrations rise, the company embraced the latter approach, says Sanghera. But TTP LabTech also wanted to avoid traditional disposable tips, as tip boxes eat up instrument deck space, and require robots to handle them.

The mosquito uses a bandolier of 36,000 disposable tips (equivalent to 95 boxes of 384 tips) on a tape reel about the size and thickness of 35-mm film. The tape feeds into the mosquito horizontally and then rotates 90 degrees to bring the tips into contact with the apparatus and samples. Each tip, like the barrel of a syringe, can aspirate, dispense, and mix reagents as needed, in volumes between 25 nl and 1.2 μ l. Once used, the tape rotates back to its original horizontal position and exits the instrument.

Though the mosquito has remained largely unchanged since its release several years ago, new applications have emerged, says Sanghera, such as real-time PCR, crystallography, and MALDI mass spectrometry sample deposition. And the user base is growing, he says; academic institutions now comprise the majority of users.

Labcyte designed its nanoliter dispensing system around a different principle.

“When you get to nanoliter volumes, you need very fine control, and that turns out to be very challenging,” says Richard Ellson, the company's chief technology officer. “It's difficult to make holes used in conventional dispensers all the same size and to make sure they do not change in size, as compounds in the screening libraries will often stick to materials.”

The Labcyte Echo 555 system overcomes these issues via a completely noncontact approach. Echo systems use sound energy to determine both the level of hydration and volume of DMSO-based samples in each well of a microtiter plate. They then focus a burst of energy customized for the fluid composition directly at the meniscus to eject precise 2.5-nl droplets into an overhanging, [continued >](#)



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The Labcyte Echo 555 system focuses a burst of energy directly at the meniscus to eject precise 2.5-nl droplets into an overhanging destination plate.

inverted destination plate, which comprises anywhere from 96 to 3,456 wells.

“As you get smaller and smaller, surface tension forces get very large in relation to gravity,” Ellson explains. “The drops stick because there’s enough surface tension to hold the drop on the ceiling of the inverted plate.” That is true even of larger volumes, he adds, which means the Echo can transfer into prefilled wells.

Multiple droplets can be ejected into a single well to achieve larger volumes, and the system is flexible enough to eject different volumes from different wells, or from a single source well into multiple destination wells.

Though the initial systems were designed specifically to handle samples in DMSO (as is common with pharmaceutical compound libraries), the systems can also be calibrated to work with aqueous samples, says Ellson. The Echo 520, to be released at this month’s LabAutomation 2008 meeting in Palm Springs, California, will have this capability out of the box, he adds.

Next Generation Pipettes

Not all liquid handling advances are robotic. Two companies have reinvented the handheld pipette itself, bringing consumer-product aesthetics to the lab bench.

Launched this past October, **Viaflo’s** Vision electronic pipettes feature a full-color LCD display and iPod-like touchwheel user interface that was consciously designed to appeal to young, technically savvy lab workers.

According to Viaflo Marketing Director Marc Hamel, the instruments score high on the “wow” scale at product shows. “It’s the first product I’ve been involved with that has real stopping power,” he says.

Users easily navigate simple menu options and set aspirate and dispense volumes using the pipette’s touch-sensitive touchwheel, just as they select songs on their MP3 player. Favorite volumes can be preset and selected for easy task-switching, and can even be beamed to the pipette from a PC via Bluetooth connectivity. And the system is programmable, with 10 commonly used pipetting modes (such as aspirate, dispense, mix, and purge) that can be used individually or linked together to build custom protocols.

Thermo Fisher Scientific has adopted another approach to simplify manual pipettes: voice-activation. Speak the words “two-three-zero” to the company’s new Matrix Hybrid Pipette, for instance, and the instrument display will read “23.0 μ l,” says Craig Weiss, director of marketing for Thermo’s Matrix Liquid Handling Products. Users can also control the volume by scrolling up and down on a digital display, or by selecting from one of a series of user-defined preset volumes.

All of which serves to increase productivity, Weiss says. “You pay some very highly educated people high dollars to do very manual labor. People are starting to see that the more you can automate that, the more it frees these highly skilled individuals to do the

core research, versus hours turning pipette knobs while pipetting by hand.”

The Air Out There

Seahorse Bioscience of North Billerica, Massachusetts, is automating an up-and-coming area of bioscience research: mitochondrial activity.

“The mitochondrion has become the focus for a whole bunch of different diseases,” says Steve Chomicz, vice president of sales and marketing. “Whether neurodegeneration, cancer, diabetes, or obesity—all the research leads them to focus on targets that involve the mitochondria.”

The best way to study that, he says, is through measurements in living cells of glycolysis and oxygen consumption, two indicators of cellular bioenergetics and mitochondrial function. And that is exactly what Seahorse Bioscience’s XF24 Analyzer does.

The XF24 uses a disposable cartridge that can be lowered just above a microlayer of cells in a microplate well to create a transient microenvironment in which changes in pH and oxygen levels can be optically detected in up to 24 wells at once. Up to four drugs can be added during this process, Chomicz says, thereby enabling experiments that are not possible using traditional oxygen-sensing equipment such as Clark electrodes and radiolabels.

“Scientists have said repeatedly that the drug delivery option is one of the most powerful features of the instrument, because you can do live agonist/antagonist measurements and dose-response curves,” says Chomicz. “That cannot be done with Clark electrodes, so they like that very much.”

Chomicz says the system software is constantly being upgraded based on user feedback, and new sensors (for instance, for glucose and CO₂) are in development.

Personal Automation

A number of companies have shifted focus from large-scale robotics down to smaller, so-called personal automation. According to Wendy Lauber, director of product management for biopharma at **Tecan**, “It is a market need to have all of the power of the high-end market with the pricing requirements of the low-end market.”

Tecan, for instance, recently released a low-end addition to its Freedom EVO line of liquid handlers, the Freedom EVO 75, which features a dual-pipetting mode “8 Plus 1 Access 8 arm,” says Lauber.

Operating in either an eight- or single-channel mode, “It gives you two functions in one, because at this low entry range, cost is a concern,” she says.

Promega is also embracing this automation trend.

“Larger liquid handlers tend to have a high learning curve, where a customer must maintain a certain level of automation expertise,” says Christopher Cowan, Promega’s integrated solutions and engineering group manager. As a result, labs are forced to keep trained specialists on staff, which is precisely the opposite of what automation is supposed to achieve, he says.

“It’s crazy: the lab is buying an open platform to increase throughput and lower the head count, and yet you need that extra head count to maintain it.”

Personal automation devices like Promega’s Maxwell 16 (released fall 2006), Cowan says, are smaller and simpler than traditional robotics systems. Just plug in the appropriate reagent cartridge—the Maxwell 16 can extract DNA, RNA, or protein from up to 16 samples simultaneously—and come back in about 30 minutes to [continued >](#)

collect your materials.

The company's second-generation instrument, released fall 2007, features a "very different and more robust design," says Cowan. More important, it can elute samples in a smaller volume (and thus, at a higher concentration); while the original Maxwell 16 extracts samples in 300 μ l, the so-called low-elution volume (LEV) protocol elutes in as little as 20 μ l.

Also entering the personal automation arena is **Qiagen**, a company that has for years sold larger-scale automation equipment.

In January 2007 the company automated its spin column-based nucleic acid sample preparation kits with the QIAcube, which can process up to 12 samples at about the same speed as a technician doing the job manually, says Wolfgang Leibinger, business director for automation.

This month, says Leibinger, the company plans to roll out the medium throughput QIASymphony, bringing the simplicity of Qiagen's earlier low throughput BioRobot EZ1 to a higher throughput audience.

The EZ1 is a relatively small, easy-to-use robot for processing nucleic acids from up to six samples at once. Simply insert a magnetic card with the protocol, add prefilled reagents, and go. Now, that simplicity is coming to the microplate level, says Leibinger, which makes such robotics more accessible.

"I see this as a major mind-shift," he says. "What we have seen in the past is if you have these complex instruments, and the guy who used it leaves the lab, the instrument is often not used anymore because no one has the confidence to work with it."

To achieve this simplicity, Qiagen departed from the typical lab robot aesthetic. The QIASymphony has a deck, for instance, but rather than dealing with it directly, users load sample kits and disposables through drawers. A robotic arm then takes the material and places it in its appropriate position. Similarly, the system has no external computer, instead relying on a touch-screen interface.

Automating Cell Culture Work

Another relatively new trend in lab robotics is cell culture automation, says Brad Nelson, director of marketing for instruments and workstations at **Velocity11**, which was recently acquired by Agilent Technologies.

Cell culture places special demands on lab automation, Nelson says. For instance, the devices must be able to fit inside a standard hood footprint and yet not disrupt the flow of air that keeps the hoods sterile.

Velocity11's Bravo liquid handler was "designed specifically to be able to operate inside a standard [laminar] fume hood," says Nelson, who notes, "if you create a device that looks like a giant block, you will disrupt the flow."

The Automation Partnership (TAP) also automates cell culture instrumentation. TAP's new Sonata, for instance, is designed to help biopharma companies evaluate and optimize cell lines and culture conditions before scaling up to larger batch sizes.

Intended as an intermediary between the research and manufacturing stages of biopharmaceutical development, the system uses parallel processing to mimic the conditions inside bioreactors, which are too large and cumbersome to optimize directly. "Sonata enables, say, 200 flasks to be incubated and for all the processing of feeding, maintenance, sampling, measuring metabolites, viability, and so on to be carried out automatically," says Rosemary Drake, director of business development.

"You get much more data, you can be more thorough, and you can reduce the time it takes to identify the best clones and culture conditions to take forward into the next phase of development," she says.

Major Vendors

Major automation vendors have not been idle, either.

PerkinElmer, for instance, continues to develop application-specific workstations based on its JANUS platform, says Nance Hall, vice president and general manager of the automation and detection solutions business. Among its new offerings are workstations specifically designed for forensics and cellular screening, as well as a new AlphaLISA Automated solution, which uses PerkinElmer's novel assay design as an alternative to enzyme-linked immunosorbent assays (ELISAs).

Unlike traditional ELISA assays, which are cumbersome and utilize several separation steps, says Hall, AlphaLISA "is a novel, no-wash technology easily automated and providing less assay variation than ELISA." By eliminating washing, AlphaLISA also removes ELISA's most time-consuming steps, she adds.

For those who need to keep all their disparate automation pieces under control, Thermo Fisher Scientific will shortly be launching a new "mover-independent" software platform, says Hansjoerg Haas, director of marketing for lab automation and cellular imaging. Such software will allow users who have robots from multiple vendors to control all of them using a single software tool, rather than with a collection of incompatible programs.

Beckman Coulter, meanwhile, has begun automating the process of flow cytometry, says Keith Roby, applications product manager for automation. "It's easy to do four or eight tubes by hand," he says. "When you start getting up to 24 tubes, it's very easy to make pipetting mistakes."

Now scale that up to 96 samples, he continues, and mistakes are inevitable. "That's where automation comes in: it will do the same thing every time; human error is taken out."

And that's a lesson that applies no matter what process you might be automating.

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