Robotic Laboratory Automation

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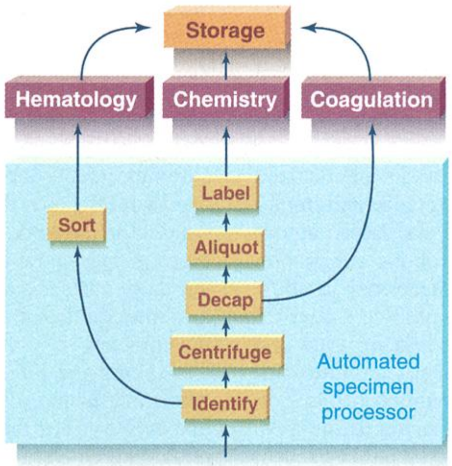
The 20th century saw the automated teller machine replace the teller at the bank, the vending machine take over from the person behind the snack counter, and electronic switchboard phase out the telephone operators of yesterday. Today, technological devices continue to assume tasks once carried out by humans because they offer major advantages in accuracy, speed, convenience, and cost. At the start of the 21st century, robotic automation is poised to revolutionize laboratory practices.

The development and patenting of the first industrial robot by Unimation, Inc. (*1*) initiated a technological revolution in robotics that, despite a few fits and starts, has largely paralleled advances in computing. This robot, called the Unimate, was first used for die-casting in 1961. Subsequent improvements in computer control and gradual reductions in the size of robots through industry and the U.S. space program developments during the 1960s and 1970s gave rise to robotic devices that were attractive for clinical laboratory applications.

Compact, microprocessor-controlled robot arms that were user-programmable were introduced in the early 1980s. The Zymark Corporation, founded in 1981, patented a robot arm with interchangeable hands that allowed development of robotic laboratory workstations capable of carrying out programmable multistep sample manipulations. The programmability of these devices allowed them to be adapted to numerous assays and sample-handling approaches. This new generation of robots was quickly applied to preanalytical sample preparation and to potency and stability testing in the pharmaceutical industry. Enterprising clinical laboratory scientists learned to program these systems to perform complex laboratory assays that are labor intensive when carried out manually, such as the estrogen receptor assay (*2*).

A laboratory formed in the early 1980s by Dr. Masahide Sasaki and his lab technologists at the Kochi Medical School in Japan provided a glimpse of the clinical laboratory of the future: robots carried test tube racks, and conveyor belts transported patient samples to various analytical workstations. Automated pipettors sipped serum from samples for the required assays. At some workstations, one-armed stationary robots performed pipetting and dispensing steps to accomplish preanalytical processing of higher complexity.



Specimen handling and analytical functions in a TLA system. Large-scale automation of the laboratory provides an automated specimen processing device that performs various preanalytical functions, including initial specimen identification, centrifugation, decapping (removal of the cap from the specimen tube), aliquoting, labeling, and sorting. An automated transportation system (depicted by the arrows) carries samples or aliquots through the needed steps in the processor and delivers them to the appropriate chemistry, hematology, or coagulation workstations. After specimen analysis, the leftover samples are carried to a long-term storage area for retrieval as needed for add-on testing, follow-up testing, or repeat testing. [Adapted from Boyd *et al.* (*5*)]

Sasaki had built his laboratory with government financial support. Starting with an empty room, he and a staff of 19 technologists designed and fabricated the mobile robot and the conveyor belt system, and they modified commercially available analyzers to draw aliquots directly from patient sample tubes on the conveyor belt (*3*). All laboratory workstations were coupled with the conveyor belts, and all workstations could operate without human intervention. The laboratory was a marvel of efficiency, performing all clinical laboratory testing for a 600-bed hospital with a government-mandated maximum staff of 19 employees. By comparison, hospitals in the United States of similar size required up to 10 times as many skilled clinical laboratory technologists. Although some of this discrepancy can be explained by a greater volume of laboratory testing, particularly emergency testing, in the United States and a lack of governmental regulations on maximum laboratory staff size, many observers saw that Sasaki's approach could dramatically reduce the cost of laboratory testing worldwide.

At about the same time, a group at the University of Virginia was developing unmanned remote laboratory units to provide near-patient laboratory testing without the need to increase laboratory staffing (*4*). Computer networking allowed personnel in the central laboratory to monitor operation of the units, perform maintenance on the instrumentation, and provide quality assurance. A robot arm for sample handling was incorporated into the unmanned laboratories. The user of the laboratory interacted with a touchscreen to identify the patient from whom the sample was obtained and to specify what analysis was desired; after entering this information, the user would then deposit the sample in a holding receptacle. The robotic arm would grasp the sample and introduce it into the clinical analyzer. After analysis, the results would be forwarded electronically to the central laboratory for review by medical technologists who would subsequently release them (electronically) to the requesting physician.

By the early 1990s, Sasaki's vision of an integrated automated laboratory, the Virginia group's demonstration of successful robotic applications, and other laboratories' successes created support for the idea of robotic automation of the clinical laboratory in the early 1990s (*5*). Enthusiasts touted the ability of robotic systems to improve the quality and reproducibility of testing, provide shorter test turnaround times, reduce costs of testing, and improve worker safety. In clinical laboratories, the Sasaki approach and its extensions (as depicted in the figure) became known as total laboratory automation (TLA), whereas remote unmanned laboratories and several hand-held clinical labo-

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ratory analyzers became known as point-of-care (POC) automation. TLA and POC were major foci for further development. The research laboratory community also became interested in robotic automation of testing protocols. Particularly important robotic laboratory automation occurred in the areas of automated gene sequencing in the Human Genome Project and in drug discovery studies in the pharmaceutical industry. Other fields relying increasingly on robotics include high-throughput proteomics and microarray technology.

Despite enthusiasm for robotic automation, several obstacles hindered its early clinical adoption. The multi–million dollar costs prevented all but the largest commercial clinical laboratories from entering the field. Some, including Metropolitan Reference Laboratories in St. Louis, Missouri, purchased robotic laboratory automation developed by Japanese firms; others, notably MDS Laboratories (Toronto, Canada) and Smith-Kline Laboratories (formerly in King of Prussia, Pennsylvania), designed and built their own. Several laboratory instrumentation vendors offered Japanese automation in North America and Europe, whereas other firms began to manufacture and market equipment designed initially by the large commercial laboratories. By the mid-1990s, however, only a handful of clinical laboratories had installed robotic laboratory automation.

A lack of standards for communications between robotics and clinical analyzers was a further obstacle to acceptance and implementation of robotic automation. Without such standards, laboratories could not easily intermix analyzers and robotic automation from different vendors. Such intermixing was necessary to allow the replacement of obsolescent analyzers, to optimize analytical processes, and to control costs. In 1997, consortia of users and vendors, working under the aegis of the National Committee for Clinical Laboratory Standards, were commissioned to develop standards for electronic interfaces and physical standards for specimen containers, specimen carriers, and bar code labeling (*6*).

Hospital clinical laboratories were slow to adopt robotic automation. Several large hospitals purchased TLA systems, relying on the automation to create "excess capacity," i.e., more test results that could be sold to others. Unfortunately, this approach did not always produce enough revenue to cover costs. Most medium-sized hospital laboratories (handling ~2500 specimens per day) had a difficult time justifying the purchase of multi–million dollar systems. Hospital administrators were understandably hesitant to be the first on the block with such expensive technology.

Pharmaceutical firms, on the other hand, invested heavily in robotic automation to increase their rate of drug discovery (*7*). Automated facilities to synthesize candidate drugs and to screen their biological effects provided three- to fivefold increases in the number of new compounds screened per unit time. Because new drugs provide the majority of income for these firms, cost-justification was easier.

In the last 5 years, manufacturers have marketed "modular" automation products that appear to be more attractive to clinical laboratories. The automation modules are directed at specific laboratory functions, including separate modules for specimen centrifugation and aliquoting, specimen analysis, and postanalytical storage and retrieval. In some systems, modules can be assembled like building blocks into a TLA system (*8*). With modular automation, a laboratory can select the module(s) that best address its needs without incurring the cost of a TLA system that might have features the lab doesn't need.

The modularization of robotic laboratory automation products is only the beginning of what promises to be a rapid evolutionary process. Some trends are already visible in clinical laboratory robotics: Fewer stand-alone robot arms are being used because robotics necessary for sampling from conveyor belts are often integrated directly into the clinical analyzers. Mobile robots that transport laboratory specimens use more sophisticated ultrasound and infrared guidance technology than early models that simply followed painted lines on the floor; these newer models can now navigate successfully through complex hospital corridors and elevators. Attention is quickly turning from the development of hardware to the design of process control software that can control and integrate the various automation components (*9*). Such software is required to manage the transport, storage, and retrieval of specimens and to support automatic repeat and follow-up testing strategies.

The future of robotic automation in the laboratory will depend on continued improvements in miniaturization (*10*). Already, hand-held POC analyzers that perform many routine chemistry, hematology, and blood coagulation assays are commonplace. Sample preparation and transport functions are performed by miniaturized robotic components incorporated directly inside these devices. Coupled with currently available radio-frequency networking facilities, POC analyzers may bring laboratory tests directly to the patient and automatically upload results to the physician's computer. Experimental devices that can perform complex genetic and chromatographic assays have been developed with the use of photolithographic techniques from the semiconductor industry. Testing with the use of POC devices costs more per test now than running a test in the central laboratory, but these costs are decreasing and near-patient testing can reduce the time required to provide potentially life-saving test results to the clinician.

Making the laboratory more portable should allow patients who must undergo frequent laboratory tests, such as those with diabetes, to exert more control over their medical care. Investigators at the University of Indiana School of Medicine described an automated device, worn on the arm, that applies a small vacuum, lances the skin, and transfers blood onto an electrochemical test strip for the measurement of glucose (*11*). Sophisticated laboratory tests will eventually be available from simple vending machines. A swipe of a credit card will activate the machine so that the desired tests can be selected at any time the patient desires. A small, robotically controlled lancet will obtain the sample from the user's finger, the analyses will be performed, and the results will be reported directly—and wirelessly—to the patient's medical record or physician's office, if desired.

After a long infancy, robotics is growing rapidly and learning to walk on its own. Investments in laboratory robot systems over the past 20 years are beginning to pay dividends of increased speed and accuracy of tests, rapid screening of potential drugs, and greatly decreased labor costs. Robotics is changing the face of medicine today and, when its potential is fully realized, promises to accomplish the seemingly impossible—reducing costs while providing individualized care to more and more patients.

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