Robots in the laboratory: a review of applications

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Abstract

Purpose – This paper aims to provide a review of the applications of robotic technology in laboratories.

Design/methodology/approach – Following a short introduction, this paper discusses a range of key applications for laboratory robots and describes a number of products. Some recent research is considered and brief conclusions are drawn.

Findings – This shows that robotic laboratory automation offers a number of key economic and operational benefits and is being used in many procedures, ranging from drug discovery and toxicity testing to forensics and environmental monitoring. An intriguing possibility is the creation of new scientific knowledge by combining robotic systems with artificial intelligence.

Originality/value – This paper illustrates the vital role played by robotic automation in laboratory procedures.

Keywords Robots, Automation, Laboratory, Analysis, Pharmaceuticals industry, High throughput screening, Artificial intelligence

Paper type Technical paper

Introduction

The use of robotics in the laboratory dates back to the early 1980s. The world's first dedicated laboratory product, the "Zymate Laboratory Automation System", dubbed the "one-armed chemist" by *Forbes* magazine, was produced by Zymark Corp. in 1982, a company founded the previous year specifically to apply robotic technology to laboratory procedures. 1984 saw the inception of automated sample preparation for drug analysis at ICI Pharmaceuticals in the UK. This was a critical development, as the needs of the pharmaceuticals industry were a key driver behind the deployment of robotic lab automation. Today, robots play a vital and growing role in all manner of laboratory procedures, ranging from routine chemical analysis to drug development and testing and DNA fingerprinting. There are several motivations for their use: in some instances they conduct highly repetitive tasks which reduces manpower and ensures uniformity; they can minimise risks to human operators by handing hazardous materials; they can eliminate sample contamination; and they can conduct certain tasks far more rapidly and with greater precision than can humans. This article reviews a range of key applications for laboratory robots.

Background and use by the pharmaceuticals industry

The pharmaceuticals industry is a major user of laboratory robots and it can be argued that the history of lab automation parallels the development of modern drug discovery within this industry. During the late 1980s and into the 1990s the industry was entering a period of high profitability but pharmaceutical companies were desperately in need of labour-saving devices as the scale and complexity of drug discovery and development was increasing dramatically. By the mid-1990s a typical drug discovery project might have involved testing several tens of thousands of compounds against a target disease but by the end of the decade, projects with 100,000 or more compounds were considered routine or even small. The only way to test these numbers of compounds within a reasonable timeframe was first to miniaturise the assays and then to automate them. Fortunately, much of the technology was already used in the medical diagnostics field and adapting it to automated drug discovery led to a new discipline termed high throughput screening (HTS). HTS systems cut the initial phase of drug discovery from several years to a matter of months and quickly found widespread acceptance among pharmaceutical companies. The key to HTS is the microtitre plate ("microplate"): a small container, usually disposable and made of plastic, that features a grid of small, open wells which act as miniature test tubes (Figure 1). Modern HTS microplates generally have 384, 1,536, 3,456 or even 9,600 wells.

Using robotics, liquid handling devices, sensitive detectors and software for data processing and system control, HTS allows millions of chemical, genetic or pharmacological tests to be conducted very rapidly. Through this process one can rapidly identify active compounds, antibodies or genes which modulate a particular biomolecular pathway and these experiments provide starting points for drug design and for understanding the interaction or role of a particular biochemical process. Several companies have developed robotic systems to handle microplates; some are established robot manufacturers who recognised HTS as a market opportunity while a growing number are specialists in

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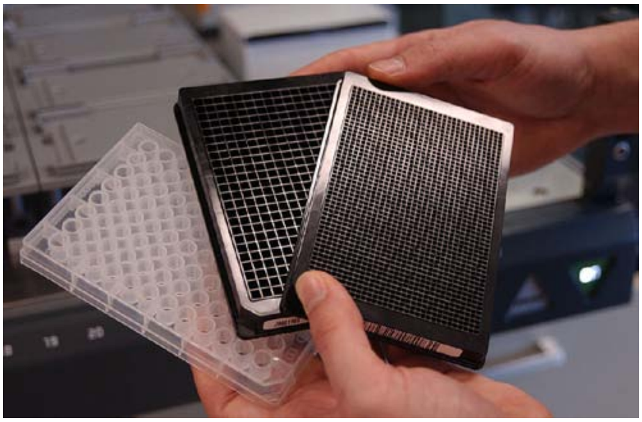
39/2 (2012) 113–119

[DOI 10.1108/01439911211203382]

Figure 1 HTS microplates



Source: Wikipedia

automated HTS and allied fields who mostly incorporate commercial robotic components into their systems. These systems (Figure 2) can conduct several pick and place operations and act as liquid handlers, which aspirate or dispense liquid samples to and from the plates but also operate as movers, which transport plates between instruments, and stackers, which store microplates during these processes. A robotic HTS system can prepare, incubate and analyse many plates simultaneously and products exist today which can test up to 100,000 compounds per day.

Unlike, say, welding or paint spraying robots, these systems are not designed to a standard format and are available in many different configurations. For eample, SSI Robotics/PaR Systems has developed a robotic HTS system that is enclosed in its own clean room, the "flexible lab automation system handler". Once microplates and other consumables are loaded, the system can run unattended for up to 24 h. The robot arm has six axes and is adapted from an industrial product. HighRes Biosolutions produces a modular system, the "MicroStar", based on Stäubli robots which is available in six-, nine- or 12-sided configurations and the "NanoCell", based on Denso robot components, is similar but has a smaller footprint. In addition to HTS in the pharmaceuticals industry, these types of product find uses in a range of other automated clinical, genomics, proteomics and molecular diagnostics applications.

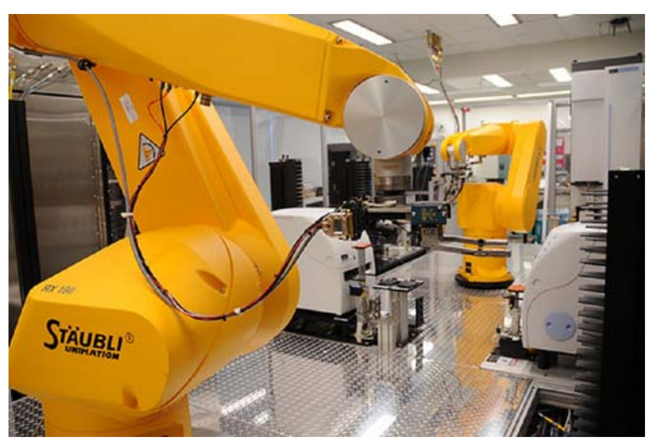
Figure 2 A robotic arm used in high-throughput screening in operation at the Southern States University

Source: Wikipedia

Toxicity testing and the search for new anti-malarial drugs

In 2008, a major initiative was set up in the USA to assess the toxicity of a large number of compounds that occur in various industrial and consumer products, including pesticides, food additives and drugs. Dubbed "Tox21", this programme involved the National Institute of Environmental Health Sciences/National Toxicology Programme, the National Human Genome Research Institute, the Environmental Protection Agency and the Food and Drug Administration. The programme has already tested more than 2,500 compounds for potential toxicity using three robots (Figure 3) but in 2011 it was announced that a new high-speed robotic screening system would be used to test around 10,000 compounds for toxicity over a range of up to 15 different concentrations. Produced by Kalypsys, Inc., the new system has been installed at the National Center for Translational Therapeutics (NCTT, formerly the National Chemical Genomics Center) in Rockville, Maryland. The system consists of a series of peripherals and workstations arranged around a central Stäubli robotic arm (Figure 4). The key components include the Kalypsys "Director" software, a pin tool for nanolitre compound transfer, plate storage and environmentally controlled assay incubation units, nanolitre reagent dispensers, a centrifuge and three different plate readers allowing the use of a variety of assay detection methods. Tests, which will include biochemical and cell-based assays, will be based on 1,536-well plates, meaning that 1,408 samples and controls can be tested on a single plate. The robot can process 100 plates each day so it could theoretically test 1 million samples in a week. According to Christopher Austin, Director of the NCTT "The Tox21 collaboration will transform our understanding of toxicology with the ability to test in a day what would take one year for a person to do by hand".

Figure 3 A robot arm (foreground) retrieves assay plates from incubators and places them at compound transfer stations or moves them to another arm (background) that services liquid dispensers or plate readers



Source: NIH Center for Translational Therapeutics

Figure 4 The "Tox21" robot system

Source: NIH Center for Translational Therapeutics

These types of robotic systems may also aid the discovery of more effective anti-malarial drugs. Again at the NCTT, robotic, ultra-high-throughput screening technology has been used to test more than 2,800 chemical compounds for activity against 61 genetically diverse strains of lab-grown malaria parasites. It was found that 32 compounds were highly effective at killing at least 45 of the 61 strains. Ten compounds had not previously been reported to have anti-malarial action and seven were more active at lower concentrations than Artemisinin, a widely used malaria drug. All the compounds are already registered as being safe or approved for use in humans or animals, although not necessarily for use against malaria. The most promising compounds identified in this work may therefore face a shorter path than usual for development into commercial anti-malarial drugs, illustrating well the importance of robot technology in this application.

DNA analysis in forensic labs

The growing use of DNA evidence has led to many forensic labs investing in robots. An explosion in the number of convicted offender samples earmarked for database inclusion and an enhanced ability to extract and successfully analyse DNA evidence from "cold cases" has led to a significant backlog with literally tens of thousands of samples waiting to be processed and analysed in some labs. Nowhere was this a more pressing problem than in the USA where, in 2000, over a million samples were awaiting DNA analysis. Such was the concern that legislation in the form of "Public Law 106-546, DNA Analysis Backlog Elimination Act of 2000" was enacted in that year. This law authorised $170 million toward reducing the backlog. Following trials with robotic liquid handling systems such as the Beckman "Biomek 2000" and Tecan "Genesis Freedom" in the early 2000s, the FBI labs, as well as several private forensic labs, are now employing robotic solutions to speed up DNA analysis. These are applied to processes such as DNA extraction, quantification, PCR set-up and post-reaction clean-up. The FBI has found that these systems can streamline repetitive tasks, improve reproducibility, reduce sample cross-contamination and allow forensic scientists to spend far less time on mundane tasks such as sample processing. The implementation of high-throughput robotics and sample-tracking software has significantly increased the number of DNA profiles generated and thus increased the potential number of investigations aided by DNA database hits. In addition, this high-throughput capacity assists other areas such as body identifications following mass disasters.

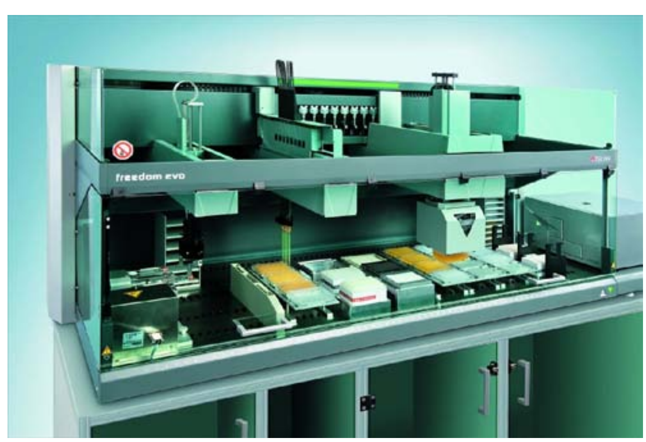
An example of a modern, robotic liquid handling system used in these applications is the Tecan "Freedom EVO". Launched in 2003, this is a highly versatile product that can be equipped with combinations of up to three independent robotic arms from a range which includes pick and place, liquid handling, multi-channel and manipulator types, together with various grippers and a variety of tip configurations. The manipulator arm extends the flexibility of the workstation by moving microplates and other labware between the worktable, peripheral devices and storage space and is available with an extended z-axis to access the space below, allowing the integration of larger items such as readers, washers, centrifuges and incubation devices. The system is shown in Figure 5.

Environmental monitoring and mineral analysis

Laboratories conducting routine analysis of environmental samples are making growing use of robotic solutions, reflecting their ability to reduce testing time and labour costs. These robots, which are frequently produced by lab analysis equipment manufacturers, can often conduct the entire analytical process, i.e. from sample preparation to measurement and data reporting and can be used for the determination of many environmental pollutants.

The determination of chemical and biochemical oxygen demand (COD and BOD) are particularly time-consuming procedures and measurements are increasingly being made with robotic systems. These are mostly small, bench-top devices and an example of a recently introduced system is the "AP 3800 multi", produced by Hach Lange. This is a robotic water quality analyser, pre-programmed for the determination of COD, together with total phosphorus, total nitrogen, ammonium, nitrate and nitrite. It is used with the company's "DR 3800" spectrophotometer and can automate procedures which include dilution, addition of reagents, mixing and digestion and can conduct multi-parameter analysis on up to 24 samples. The key robotic component is the multifunctional arm which is used for gripping, transporting, stirring and pipetting. The "SP100" from Skalar Analytical BV is a robotic analyser that can determine several variables including

Figure 5 The "Freedom EVO" robotic handling system



Source: Tecan Group AG

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COD and BOD, as well as pH, conductivity, alkalinity, carbonate/bicarbonate, turbidity and colour. The BOD variant is aimed at labs running over 100 BOD tests/day and features two manipulators and a sample transport mechanism. The samples, which are loaded in racks, are presented via a rail mechanism to the manipulators, which in turn perform tasks such as stirring; addition of dilution water, seed and nitrification inhibitors; bottle capping and de-capping; and oxygen measurements. The Windows software controls the measurements, creates worksheets, calculates the results according to various standards (e.g. EPA, ISO, DIN, etc.) and generates reports.

Analysing mineral ore samples for metal content is an example of where lab robots can reduce the exposure of human operators to hazardous chemicals. Typically, a four-acid digestion process is required to dissolve the ore and involves hydrochloric, nitric, hydrofluoric and perchloric acids, all of which pose a real danger. Robotic ore preparation systems perform a sequence of chemical additions, weighing, heating, cooling, mixing and cleaning actions which comprise the digestion process. This yields a liquid which can subsequently be analysed for metal content using techniques such as atomic absorption spectroscopy or inductively coupled plasma mass spectrometry. An example of a commercial product is the "Acid Digest Robot Laboratory System" produced by Australian robotics and automation specialists Argon Technology Pty Ltd This features two suitably protected seven-axis robotic manipulator arms (Figure 6), thermal heating blocks and the control software. A similar system is used to prepare gold-containing sample for analysis which involves aqua regia, an exceedingly hazardous mixture of concentrated hydrochloric and nitric acids.

Beyond lab automation: robotic scientific discovery

While all of the previous examples concern varying forms of robotic automation, research conducted by the Computational Biology Group (CBG) at Aberystwyth University in Wales with colleagues from the University of Cambridge has taken this process to a new level by using artificial intelligence and robotics to make scientific discoveries. Dubbed the "Robot Scientists", the first prototype, "Adam", has proven the potential of this approach by identifying 12 genes responsible for catalysing specific reactions in the metabolic pathways of the yeast *Saccharomyces cerevisiae*. The CBG concept uses techniques from artificial intelligence to automate all aspects of the discovery process: it generates hypotheses from a computer model of the domain, designs experiments to test these hypotheses, runs the physical experiments using robotic systems, analyses and interprets the resulting data and repeats the cycle. The system uses a concept termed hypothesis-driven, closed-loop learning (Figure 7) and Figure 8 shows the robot's various components. These includes three incubators, two liquid handlers, a microplate washer, a microplate centrifuge, three robot arms, two microplate shuttles, two barcode readers, two plate readers and several PCs. All the equipment is integrated via controlling software on the PCs. The complete system is physically protected by a perspex enclosure which is fed with filtered air which keeps it at positive pressure to minimise cross-contamination.

Figure 6 Laboratory robots conducting an acid digestion process

Source: Wikipedia

The second Robot Scientist, "Eve", was commissioned in early 2009, although both the software and biological assays are still under development. The aim is to demonstrate the automation of closed-loop learning in drug screening and design by integrating machine learning with a technique termed automated quantitative structure-activity relationship (QSAR), a field of computational chemistry whereby a chemical structure is quantitatively correlated with a well-defined process such as biological activity or chemical reactivity. Eve's robotic system is capable of moderately high-throughput screening (i.e. greater than 10,000 compounds per day) and is designed to be sufficiently flexible to be reconfigured rapidly to conduct a various different biological assays. The system will start by performing a standard mass-screen against the target assay, monitoring the results in real time, and when sufficient hits are found it will stop the process. After verifying the hits, it will then switch to a more targeted approach using machine learning and QSARs to look at the chemical structures of the identified compounds and generate hypotheses about which it considers would be the most useful to test next. It then plans the screening experiments to test these hypotheses, runs the experiments on the robotic system, uses machine learning to analyse these results and then iteratively cycles around testing other compounds until it can identify the best set of lead compounds for the target. Eve will initially test those compounds which are available from its own compound library, then suggest other compounds that are commercially available that should be tested from an automation-accessible library of 14,400 chemical compounds termed the Maybridge "HitFinder" library. It is recognised that this is not large by industrial standards; a pharmaceutical company may have many hundreds of thousands or even millions of compounds in its primary screening library. However, the aim is to demonstrate that incorporating machine learning and QSARs into the screening process can improve on the current mass-screening approach. Ultimately, however, Eve might even be able to suggest new compounds that should be synthesised for testing. Figures 9 and 10 show a schematic and photographs of the Eve system, respectively.

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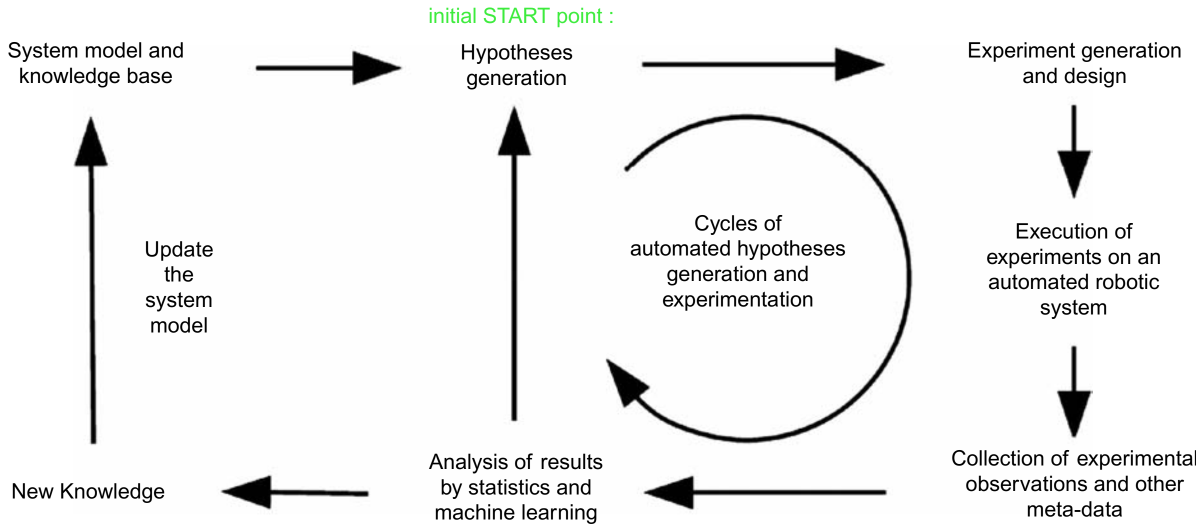
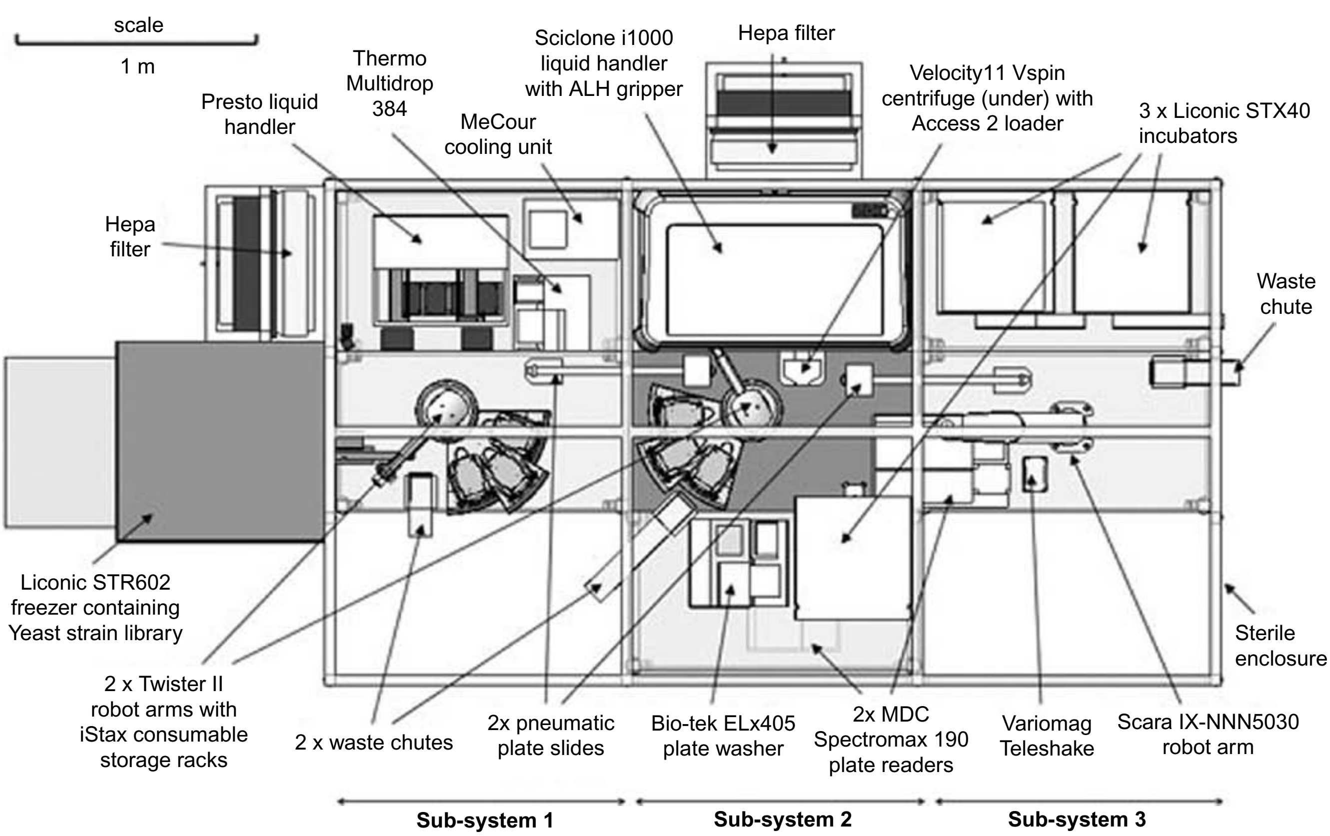
Figure 7 Hypothesis-driven closed-loop learning



Notes: This shows how iterative cycles of hypothesis-driven experimentation allow the autonomous generation of new scientific knowledge
Source: Sparkes *et al*. (2010), *Automated Experimentation*, 2:1. doi:10.1186/1759-4499-2:1

Figure 8 Schematic of the "Adam" robotic system



Source: Courtesy of CBG, Aberystwyth University

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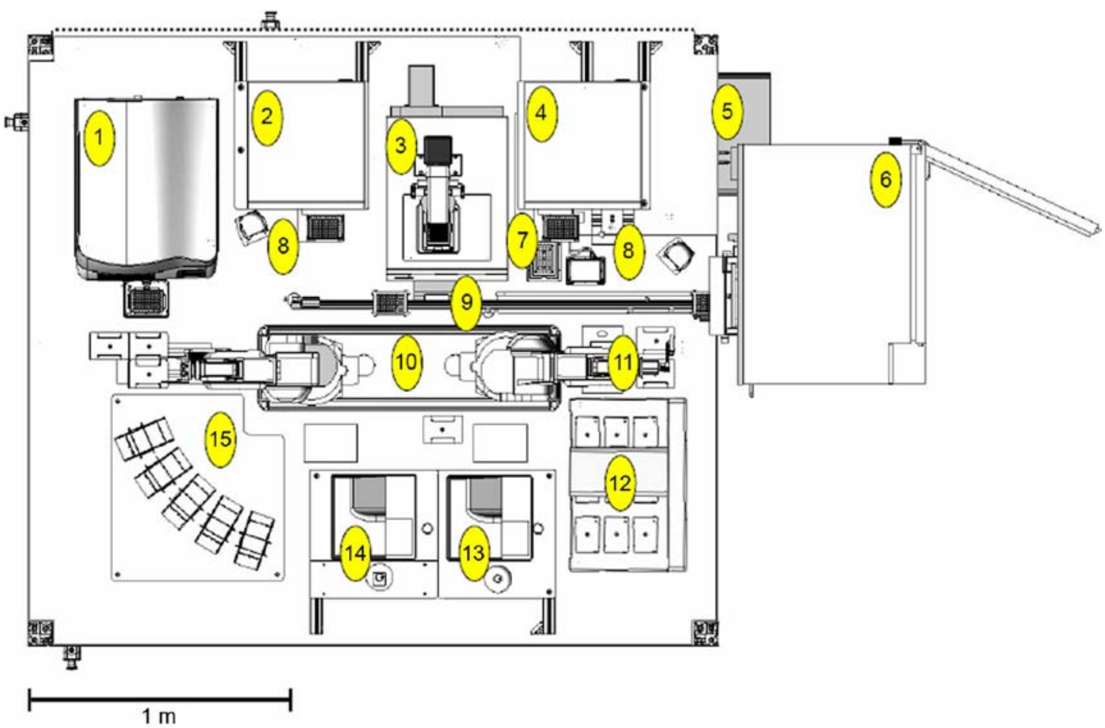
Figure 9 The "Eve" robotic system

(a) **(b)**

Notes: (a) An external view, also showing Adam at the extreme left; (b) manipulator arm and some of the instruments in the system
Source: Sparkes *et al*. (2010), *Automated Experimentation*, 2:1. doi:10.1186/1759-4499-2:1

Figure 10 Schematic of the "Eve" system



Notes: 1 – acoustic liquid handler, 2 – microplate reader, 3 – cellular imager, 4 – microplate reader, 5 – incubator, 6 – dry store, 7 – fluid capper/recapper, 8 – two plate shakers and two barcode readers, 9 – linear actuator track, 10 – robot plinth holding two Mitsubishi robot arms, 11 – tube rack 2D barcode scanner, 12 – liquid handler, 13 – liquid dispenser, 14 – two further liquid dispensers and 15 – consumables stacks for microplates, tube racks and tips; there are also two computers controlling the robotics, plus a networked computer server which runs all the other codes vital to Eve's function
Source: Sparkes *et al*. (2010), *Automated Experimentation*, 2:1. doi:10.1186/1759-4499-2-1)

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Conclusions

Robotic automation is being used in many laboratory procedures and can yield benefits which include reduced manpower, greater uniformity and precision, minimised risks to human operators, the elimination of sample contamination and the ability to conduct certain tasks far more rapidly than possible by manual means. The pharmaceuticals industry's needs for more rapid drug discovery and screening catalysed the early deployment of laboratory robots and it is fitting that the research discussed above may, in the fullness of time, yield unique drug discovery technologies for use by this industry.

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