AUTOMATION BY LABORATORY ROBOTICS IN PHARMACEUTICAL RESEARCH INDUSTRY: A LATEST VENTURE IN INNOVATIVE IDEA

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ABSTRACT

Robots in laboratory, life science and pharmaceutical applications perform tasks at rates beyond human capability. These robots function in potentially hazardous settings in proximity to biological dangers, the threat of radioactive contamination and toxic chemotherapy compounds. Robotics is called upon to assemble and package a variety of medical devices and implants as well as preparing prescriptions for mail-order pharmacies or hospitals. Robots are doing assay analysis and automating the movement of test tubes in research laboratories. Because of the high number of samples that need analysis and the amount of data collection required, the process and costs are easily validated with robotics. In pharmaceutical applications, hospitals use robots to mix potentially hazardous cancer drugs and those associated with radiation. The Laboratory Robotics Interest Group (LRIG) is an international non-profit organization dedicated to the study and discussion of laboratory automation. LRIG activates the uses of laboratory automation in high-throughput screening, drug discovery, combinatorial chemistry, chemical synthesis, compound purification, compound distribution, data management, pharmaceutical dosage form sample preparation, dissolution testing, bio analytical technology, chemical analysis, solid phase extraction, validation and product formulation.

Keywords: Automation, Accurate, Flexible, Robust, Compact, Efficient, Easy to Use.
INTRODUCTION

Laboratory robotics is the act of using robots in biology or chemistry labs. For example, pharmaceutical companies employ robots to move biological or chemical samples around to synthesize novel chemical entities or to test pharmaceutical value of existing chemical matter.\textsuperscript{1,2} Advanced laboratory robotics can be used to completely automate the process of science, as in the Robot Scientist project.\textsuperscript{3}

Laboratory processes are suited for robotic automation as the processes are composed of repetitive movements (e.g. pick/place, liquid & solid additions, heating/cooling, mixing, shaking and testing).

Automated synthesis originated with peptide and oligonucleotide synthesis. One early example is the polymerase chain reaction (PCR) which is able to amplify DNA strands using a thermal cycler to micromanage DNA synthesis by adjusting temperature using a pre-made computer program. Since then, automated synthesis has been applied to organic chemistry and expanded into three categories: reaction-block systems, robot-arm systems, and non-robotic fluidic systems.\textsuperscript{4}

![Figure-1: Laboratory robot in operational research](image)

The primary objective of any automated workbench is high-throughput processes and cost reduction.\textsuperscript{5} This allows a synthetic laboratory to operate with a fewer number of people working more efficiently.

Biological and chemical samples, in either liquid or solid state, are stored in vials, plates or tubes. Often, they need to be frozen and/or sealed to avoid contamination or to retain their
biological and/or chemical properties. Specifically, the life science industry has standardized on a plate format, known as the microtiter plate, to store such samples.\textsuperscript{6}

The microtiter plate standard was formalized by the Society for Biomolecular Screening in 1996.\textsuperscript{7} It typically has 96, 384 or even 1536 sample wells arranged in a 2:3 rectangular matrix.

The standard governs well dimensions (e.g. diameter, spacing and depth) as well as plate properties (e.g. dimensions and rigidity). A number of companies have developed robots to specifically handle SBS micro plates. Such robots may be liquid handlers which aspirates or dispenses liquid samples from and to these plates, or "plate movers" which transport them between instruments. Other companies have pushed integration even further: on top of interfacing to the specific consumables used in biology, some robots have been designed with the capability of interfacing to volumetric pipettes used by biologists and technical staff.

Essentially, all the manual activity of liquid handling can be performed automatically, allowing humans spending their time in more conceptual activities.\textsuperscript{8} Instrument companies have designed plate readers which can carry out detect specific biological, chemical or physical events in samples stored in these plates. These readers typically use optical and/or computer vision techniques to evaluate the contents of the microtiter plate wells.

One major area where automated synthesis has been applied is structure determination in pharmaceutical research. Processes such as NMR and HPLC-MS can now have sample preparation done by robotic arm.\textsuperscript{9} Additionally, structural protein analysis can be done

**Figure-2: Laboratory robots in scientific job**
automatically using a combination of NMR and X-ray crystallography. Crystallization often takes hundreds to thousands of experiments to create a protein crystal suitable for X-ray crystallography. An automated micropipette machine can allow nearly a million different crystals to be created at once, and analyzed via X-ray crystallography.

**Combinatorial Library Synthesis**

Robotics has applications with Combinatorial Chemistry which has great impact on the pharmaceutical industry. The use of robotics has allowed for the use of much smaller reagent quantities and mass expansion of chemical libraries. The "parallel synthesis" method can be improved upon with automation. The main disadvantage to "parallel-synthesis" is the amount of time it takes to develop a library; automation is typically applied to make this process more efficient.

![Laboratory robots in technical mood](image)

The main types of automation are classified by the type of solid-phase substrates, the methods for adding and removing reagents, and design of reaction chambers. Polymer resins may be used as a substrate for solid-phase. It is not a true combinatorial method in the sense that "split-mix" where a peptide compound is split into different groups and reacted with different compounds. This is then mixed back together split into more groups and each group is reacted with a different compound. Instead the "parallel-synthesis" method does not mix, but reacts different groups of the same peptide with different compounds and allows for the identification of the individual compound on each solid support. A popular method implemented is the reaction block system due to its relative low cost and higher output of new compounds compared to other "parallel-synthesis" methods. Parallel-Synthesis was developed by Mario Geysen and his colleagues and is not a true type of combinatorial synthesis, but can be incorporated into a combinatorial synthesis. This group synthesized 96
peptides on plastic pins coated with a solid support for the solid phase peptide synthesis. This method uses a rectangular block moved by a robot so that reagents can be pipetted by a robotic pipetting system. This block is separated into wells which the individual reactions take place. These compounds are later cleaved from the solid-phase of the well for further analysis. Another method is the closed reactor system which uses a completely closed off reaction vessel with a series of fixed connections to dispense. Though the produce fewer number of compounds than other methods, its main advantage is the control over the reagents and reaction conditions. Early closed reaction systems were developed for peptide synthesis which required variations in temperature and a diverse range of reagents. Some closed reactor system robots have a temperature range of 200°C and over 150 reagents.

**Purification**

Simulated distillation, a type of gas chromatography testing method used in the petroleum, can be automated via robotics. An older method used a system called ORCA (Optimized Robot for Chemical Analysis) was used for the analysis of petroleum samples by simulated distillation (SIMDIS). ORCA has allowed for shorter analysis times and has reduced maximum temperature needed to elute compounds.\(^\text{13}\) One major advantage of automating purification is the scale at which separations can be done.\(^\text{14}\) Using microprocessors, ion-exchange separation can be conducted on a Nano liter scale in a short period of time.

Robotics has been implemented in liquid-liquid extraction (LLE) to streamline the process of preparing biological samples using 96-well plates.\(^\text{15}\) This is an alternative method to solid-phase extraction methods and protein precipitation, which has the advantage of being more reproducible and robotic assistance has made LLE comparable in speed to solid phase extraction. The robotics used for LLE can perform an entire extraction with quantities in the microliter scale and performing the extraction in as little as ten minutes.

![Figure-4: Laboratory robots in analytical research lab](image-url)
Advantages and Disadvantages

Advantages
One of the advantages to automation faster processing, but it is not necessarily faster than a human operator. Repeatability and reproducibility are improved as automated systems as less likely to have variances in reagent quantities and less likely to have variances in reaction conditions. Typically productivity is increased since human constraints, such as time constraints, are no longer a factor. Efficiency is generally improved as robots can work continuously and reduce the amount of reagents used to perform a reaction. Also there is a reduction in material waste. Automation can also establish safer working environments since hazardous compounds do not have to be handled. Additionally automation allows staff to focus on other tasks that are not repetitive.

Disadvantages
Typically the costs of a single synthesis or sample assessment are expensive to set up and startup cost for automation can be expensive. Many techniques have not been developed for automation yet. Additionally there is difficulty automating instances where visual analysis, recognition, or comparison is required such as color changes. This also leads to the analysis being limited by available sensory inputs. One potential disadvantage is an increases job shortage as automation may replace staff members who do tasks easily replicated by a robot. Some systems require the use of programming languages such as C++ or Visual Basic to run more complicated tasks.\textsuperscript{15}

CONCLUSION
In medical device manufacturing, robotics plays an active role in assembly. The manufacturing process is highly regulated and must be approved by the Food and Drug Administration (FDA). Manufactures use robotics to reduce cost. Robotics performs important tasks in surgical procedures. Tele-operated surgical robotics is used to augment the surgeon. Robots are used for delivery of radiation and for proton therapy. The goal is to administer the smallest dose of radiation as possible to the precise location. Robots are very precise, positioning equipment and patients accurately in three-dimensional space. Robots are loading and unloading injection moulding machines, assembling medical devices and polishing implants. In pharmaceutical production, robots handle bottles in the cell culture process, loading and unloading autoclaves and packaging machines, as well as de-nesting syringe tubs. Applied Manufacturing Technologies Inc. (AMT, Orion, Michigan) works with
companies that produce dental appliances. Jordan Merhib, AMT’s Director of Business Development, describes a typical application. A dental appliance manufacturer uses several robots primarily for sorting and packing at the end of the production line. Another company making personal medical devices and eyeglasses use robots for machine tending, loading raw materials into machines and unloading finished product. Personal medical devices have many unique parts and their assembly and packaging is especially suited to robotics. Robots help researchers perform a sufficient number of experiments to ensure valid conclusions. A robotic micro-array can put 40,000 dots of deoxyribonucleic acid (DNA) no more than 75 microns in diameter onto a single slide. That cannot be done with a human hand. Using vision, a robot can identify an object of interest on a petri dish. In cloning, robotic vision identifies what part of the colony bacteria comes from. Vision helps identify the quality of the bacteria and helps direct the robot with special tooling to move the high quality bacteria into another petri dish. Vision is used to identify what part of the colony needs removal for different processing or for disposal. Robotics has a certain future in laboratory, life science and pharmaceutical applications. There is increased activity for bench-top robotics performing various protocols. These stations are reprogrammable and many are complex. Robotics is essential to modern scientific or commercial research and experimentation.

REFERENCES