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Liquid Handling Technologies: A Study Through Major Discoveries and Advancements

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Abstract
Liquid handling is an essential process in laboratories involving automatically transferring accurate amounts of liquids for various task completions such as sample preparation, pipetting, dilution, and mixing. Automated liquid handling systems (ALHS) help to minimize the errors, complications, and difficulties that are faced with manual methods of liquid handling by efficiently enhancing the accuracy, precision, and reproducibility of experimental workflows and have transformed life sciences aiding research in various fields. Processes like Nuclear Magnetic Resonance (NMR) spectrometry, mass spectrometry, and acoustic droplet ejection with ALHS showcase tremendous potential. Outdated manual machinery is being replaced rapidly with automated tools. We have observed that these laboratory setups are sophisticated and costly. It is challenging to access such technologies, especially in poor or developing countries. At the nanoscale level, handling and evaporation of biomaterials becomes a great issue. Multitudinous devices can combat the cost issue along with utilization of single equipment without the enhancement of add-on modules. Liquid handling devices enhance the quality of experiments contributing to efficient dealing of circumstances like COVID-19. They aid in genomics and proteomics and play a pivotal role in liquid manipulation, drug screening, quantifications, forensic studies and many more. Liquid handling devices with robotic equipment can perform multiple tasks and can assist in a wide range of fields. We anticipate that in the coming years, our laboratories will be furnished with advanced, robotic technologies and cause a revolution in the scientific scenery.

Keywords: Automated liquid handling, Drug discovery, Proteomics, Molecular Biology

Introduction

The creation of automated liquid handling systems (ALHS) has been aiding researchers in various fields of life sciences such as molecular biology, drug development, genomics, and proteomics by enhancing the efficiency, accuracy, reproducibility of experimental workflows, reducing cost, time, and error and addressing several critical bottlenecks associated with manual liquid handling devices. Currently, technologies such as Filter-aided sample preparation (FASP) [1], NMR Spectrometry [2], mass spectrometry [3], acoustic droplet ejection [4], lateral flow assays (LFA) [5], and

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Electrochemiluminescence [6] can be integrated with ALHS for better performance. New systems and devices are also emerging further enhancing experimental processes [7]. According to a report, the global market size for automated liquid handling was 1,181.82 million USD in 2022 and by 2032 The projected market size is estimated to reach approximately USD 2,580.45 million [8]. According to another report, the market size of automated liquid handling is estimated to grow to USD 6.34 billion by 2035 from USD 2.82 billion in 2023 [9]. These reports show that there is a great demand for automated liquid handling and the demand is going to increase.

The introduction of ALHS in the study of protein, gene, drug, and pharmaceutical industries has enabled laboratories to find compounds and drugs at a rate previously unprecedented [10]. Homo sapiens have 19,116 protein-coding genes [11]. There are other species that have more than that. Because of that, many experiments need to be performed to determine the structure, function, quantification, and identification of proteins present in an organism [12]. In the pharmaceutical industry, 200,000 to one million compounds are screened for a single project. Moreover, only 10% of small molecule projects might find candidates that can enter the clinical phase [13]. Automation has freed up researchers from tedious and time-consuming tasks so that they can focus on higher-level tasks [12]. In the field of genetics, automated liquid handling systems are being used to perform applications such as DNA extraction, purification, isolation, sequencing, genotyping, and preparing bioactive arrays. ALHS also carries out protein purification, crystallization, expression, and various other proteomics applications [07].

The evolution of the tools at hand and the introduction of projects like Quality by Design and Process Analytical Tools also assisted scientists in having a better understanding of the process and a clear definition of the design space [14]. The increasing computational power helped researchers to use more complex modeling tools, freeing them from the heuristic modeling chains that, although useful, rarely allow for further predictions and do not promote process understanding. As the industry grew, High-Throughput Process Development (HTPD) combined High-Throughput Screening (HTS), a greater mechanical ability to understand processes, and a higher computational capability for smarter process development, which aided experimentations for cost-effective and time-efficient quality performance [14].

While several researches have been conducted on the specific applications of automated liquid handling systems and the state-of-the-art technology currently available in the market, an overall picture of the impact of these technologies globally in various areas of life sciences is yet to be focused upon.

The purpose of this study was to review the recent advancements in automated liquid handling techniques for various applications such as proteomics, drug development, and bioactive assays within molecular biology and to focus on the accessibility of these world-class technologies across all nations and institutions worldwide.

Discussion

Manual versus Automated Techniques

Manual processes of liquid handling being traditionally used in laboratories are prone to errors, inaccuracy, variability, and can be time-consuming. Automated liquid handling systems are much more precise as they eliminate the likelihood of human errors. Manual processes commonly used in

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laboratories include:

Pipetting

One of the essential tools in biomedical and analytical laboratories, analogous to workstations for computer sciences are pipettes. A large number of variations in the pipetting method exist but most of them are unknown as there have not been many research studies conducted on the extent of these variations in practice. Pipetting is a technique in laboratories for measuring and transferring very precise amounts of volume from one container to another. Accuracy and precision are the most critical measures for the validity and reliability of an assay. Inconsistencies in either or both measures can lead to errors which will eventually end up affecting the reliability, validity, and quality of the research findings. When the pipetting technique is performed manually the chances of skewed research findings increase. With the strong need for quality. The quality assurance and reliability of these assays are highly dependent on these factors. With the strong need for quality assurance, many international bodies have made available materials as well as reporting guides. As accuracy and precision are the most important factors it is crucial to assess and determine the performance characteristics. They can be evaluated using bioanalytical approaches [15].

Dilution

Dilution of mixing another solution with a solvent to reduce its concentration. Manual dilution is a technique used in laboratories. It is a process in liquid handling used to achieve desired concentrations in stock solutions, and sample preparation for many assays and research. Dilution serves multiple essential functions such as sample mixing with certain reagents at specific dilution ratios, reducing sample matrix effects, and bringing target analytes within the linear assay detection range, among many others. In traditional laboratory settings, the sample processing is performed through automated or manual pipetting. When working with limited resources, neither skillfully trained personnel nor proper laboratory equipment are available which limits the availability of quality diagnostic tests. Manual dilution methods such as manual pipetting involve handheld pipettes to measure and transfer the liquids. This requires skilled and trained personnel to perform accurately. By manually diluting the results are more likely to have errors. For an accurate quality diagnosis, we require skillfully trained personnel and laboratories with proper equipment, but around the world at places where such types of resources are not available, the diagnosis is more prone to contain errors and inaccuracy [16]. At places where properly equipped laboratories are not available manual dilution methods such as manual pipetting are preferred. These methods are manually practiced for the measurement and dilution of liquids.

Mixing

In liquid handling, mixing is a very crucial step in order to ensure that all the components in the solution or sample are equally distributed throughout the sample or solution. Homogeneous mixing of liquids is essential for assays, reactions, and sample preparation. Manual stirring, vertexing, and automated mixing are the methods of mixing. Keeping quality assurance in mind manual processes of mixing aren't the best as they increase the high risks of the occurrence of errors [16].

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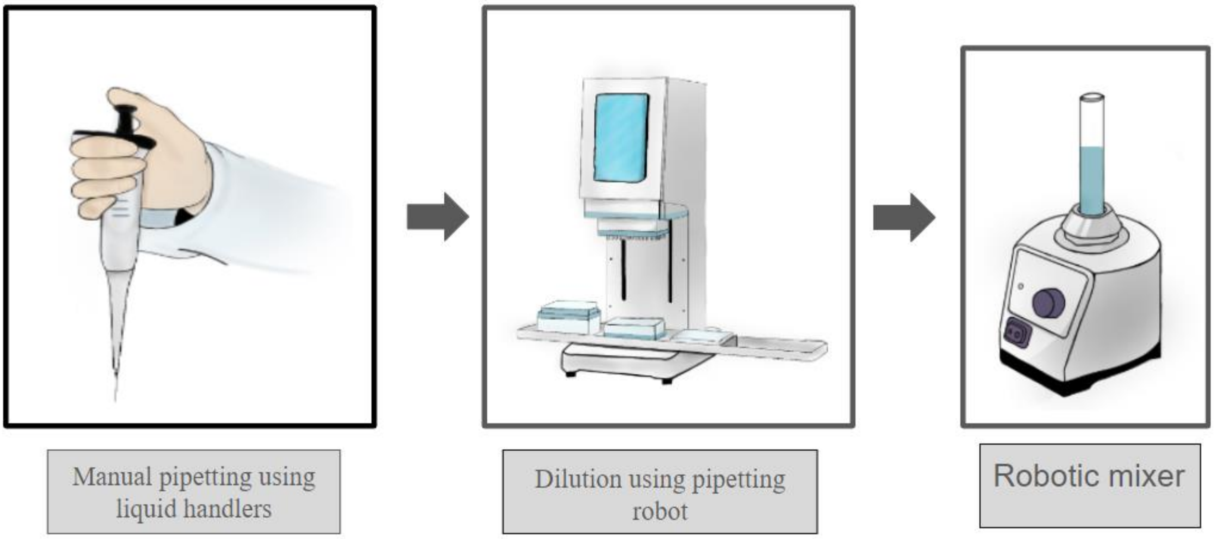

Figure 1. Liquid handling processes and their equipment

Applications in Proteomics and Drug Discovery

A set of proteins expressed by a genome is known as proteome and the study of proteome is proteomics. Proteomics has great importance in biomedical research [17]. Plasma proteomics can help detect various types of disease by identifying biomarkers. Bottom-up techniques are widely used for analyzing plasma. However, the complexity of plasma introduces significant analytical challenges [18]. It is time-consuming, and tiresome to analyze hundreds of plasma samples [19]. Introducing Automated liquid handling systems can streamline the processes [20].

One of the most important things about sample preparation protocol for testing is the reproducibility of extraction, solubilization, and digestion of proteins. In Automated filter-aided sample preparation (FASP) protocols, protein samples are trapped, denatured, reduced, alkylated, and digested with trypsin. Then mass spectrometry is used to analyze peptides. Buffer exchanges are performed by controlling the vacuum pressure using bovine serum albumin (BSA). The optimized parameters are assessed utilizing tissue samples with both manual and automated FASP protocols and the eluted peptides were subjected to analysis using liquid chromatography. Automatic liquid handlers can be incorporated into most of the steps. Automated filter-aided sample preparation (FASP) protocol can significantly reduce both the time and cost of analysis. Furthermore, it is capable of handling large sample sets in a reproducible and quantifiable manner [1].

NMR Spectrometry and Mass spectrometry is a crucial part of studying proteins. NMR Spectrometry is used for studying the molecular structure, folding, and behavior of proteins [21]. For loading samples into an NMR probe, an automated system can be used. It can increase throughput and improve sample utilization. The molecular weight of proteins is determined using Mass spectrometry which measures the mass-to-charge ratio [21]. Preparing samples for mass spectrometry-based proteomics can be burdensome and time-consuming, leading to potential analytical errors. Integrating automatic liquid handling robots into most labor-intensive steps can be used in large-scale and high-throughput mass spectrometry sample processing [3]. Automating most repetitive and labor-intensive tasks and enhancing accuracy and reproducibility for large numbers of samples require the following features : [1] time-controlled liquid transferring with accuracy, [2] liquid transferring from reagents vials or plates to digestion plate, [3] 96/364 pin and 8-span head, [4] grippers to move the digestion plate, [5] temperature and time-controlled incubator with shaking ability, and [6] an independent plate shaker designed for use as a mixer [03]. Automated liquid handling workstation can also be integrated into Immunoaffinity chromatography which can increase the sensitivity of less abundant proteins and separate them [23].

Liquid handling robots for pipetting reagents are utilized to streamline the process of setting up assays in scientific research environments, such as biochemical assays, antibody-based assays, molecular assays, and crystallography studies to determine enzyme structure and function. They have the advantage of increased reproducibility and accuracy compared to their manual counterpart. reproducibility and accuracy are requirements for better PCR results. Even small errors in the dispense accuracy can lead to significant variations after amplification [24].

Microbeads functionalized with biomolecules are also very helpful in various biological assays. But preparing microbeads is tedious, and time-consuming [25]. This can also cause human error which can compound and result in inadequate preparation [26]. Trained personnel are also required for manual processes like repeated pipetting, washing, liquid exchange, centrifugation, and mixing. There are robotic systems that can automate the attachment of biomolecules to microbeads and successfully produce functionalized microbeads. They can remove bottlenecks and sources of error. These systems can also be modified for solid-phase synthesis or functionalizing cells [25].

The utilization of medium-throughput to high-throughput robotic screening in specialized assays is a standard practice in the pharmaceutical industry [27]. Many reagents used in drug discovery can have unknown hazards and automated liquid handling systems can minimize that risk. Utilizing robotic systems in chemical synthesis can increase throughput, reduce time, and lower the consumption of materials [28].

It is advantageous to minimize sample volumes to the nanoliter scale to conduct high-throughput screening experiments cost-effectively, surface acoustic waves, pin tools, high-speed flow sensors, and electromagnetic bellows are some of the instruments that can handle low-volume samples with precision and accuracy. Although these are helpful in many situations they can also be costly. Pocket Tips can be an economical solution. It contains a specific pocket with consistent dimensions which captures and then releases nanoliter volumes of liquid. It can also be incorporated into existing liquid-handling platforms which lack the capability of performing low-volume dispensing [29].

Another low-volume dispensing technology is Acoustic droplet ejection (ADE). This is a contactless dispensing technology that is used in life science research and development and has the capability of transferring liquids in nanoliter and picolitre volumes using focused acoustic energy [30]. This tool is well-accepted in chemical synthesis [28]. This technology can easily be automated, and the transfer process is precise and reliable [30]. This technology does not require tip washing, eliminating any possibility of cross-contamination, unlike conventional contact liquid dispensers. This technology can reduce the amount of materials needed leading to savings in cost [31]. This technology is compatible with other flat-bottomed storage containers. Volatile, corrosive, and viscous liquids can be dispensed using this technology [30].

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Advancements in Liquid Handling Technologies

In recent years, laboratory automation has become quite popular, and robotic technologies that have been in the field of factory automation for a long time are used for automatic liquid handling. New application-based devices continuously emerge for this purpose [07]. Advances in molecular biology, human genetics, and functional genomics produce increasing numbers of targets to study. This has fueled a need for advanced detection and screening capabilities.

In the biotechnological field, the advancement of experimental approaches prioritizes less time and minimizes errors. High-throughput platforms have revolutionized the accomplishment of multiple laboratory protocols in a fully automated manner, which is well for individual procedures and screenings. TECAN EVOware software is a robotic platform that ensures optical pipetting performance especially important for biopharmaceutical applications. It has a liquid glass editor module allowing the customization of pipetting parameters for each pipetted liquid [33]. The Freedom EVO 200 is equipped with a TeVacS two-position vacuum filtration manifold, an 8-channel liquid handling arm with stainless-steel tips and a built-in capacitance function [34]. This highly customized robotic setup provides a workstation for performing fully automated sample preparation from sample tubes to the prepared 96-well plate ready for injection. [35]. Recent advancements in the system have provided a continuous flow during a defined chromatography by eliminating wasteful time. The Tecan Freedom EVO 200 workstation has aided in high-throughput protein production systems. This has contributed to the structural and functional studies of proteins and has contributed to a massive amount of results [36].

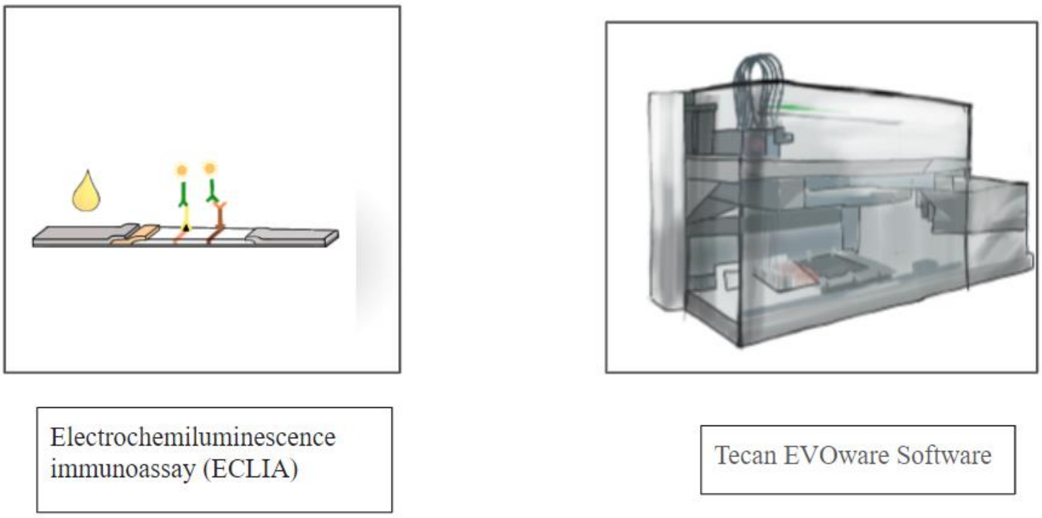

Figure 2. Recently developed liquid handling technologies

Lateral Flow Assay (LFA) is a diagnostic technology that has enabled the detection of pregnancy hormones, environmental toxins, infectious diseases, etc. at a low cost and without high demands [05]. This is a paper-based platform [36] that can detect a variety of samples Including urine [37], saliva [38], serum [39], and plasma [40]. A lateral flow assay consists of a chromatographic system and immunochemical reaction (between antibody-antigen, nucleic acid, and target analyte). A lateral flow assay (LFA) is made up of four parts: 1) a sample pad, which is the area on which the sample is dropped; 2) a conjugate pad, on which labeled tags are combined with biorecognition elements; 3) a reaction membrane containing test line and control line for target DNA-probe DNA hybridization or antigen-

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antibody interaction; and 4) absorbent pad, which reserves waste. For the construction of LFAs gold nanoparticles, enzymes, etc. are used as a label for increasing the sensitivity [41]. Lateral flow tests provide a very simple platform for the rapid detection of substances to be analyzed. From an engineering and manufacturing point of view, the high flexibility along with combining various membrane components via a simple lamination process makes lateral flow technology a viable platform that is also cost-effective for applications in the diagnostics of various diseases, pregnancy hormones, food, and water safety, pharmaceutical analysis and drug testing. In addition, emerging applications of lateral flow strip tests are now being used for the detection of nucleic acid in the form of DNA probes and aptamers [42]. Electrochemiluminescence or electrogenerated chemiluminescence involves the electron transfer reactions of electro-generated species to form excited states that emit light. It is a very powerful tool for sensing and imaging due to its integration of electrochemical and spectroscopic techniques. Recently ECL immunoassay has received a lot of attention and is now being extensively used in clinical analysis. It has been shifted from a single-signal output to a multiple-signal output to combat insufficient disease diagnosis or prediction. ECL imaging analysis is a fast-developing technology in bioanalysis with resolutions belonging to both space and time, high throughput screening, and visualization features [06]. Recent advancements have called for more sophisticated research tools and workstations. However manual assembly of such large numbers of devices is time-intensive, error-prone, and costly. This

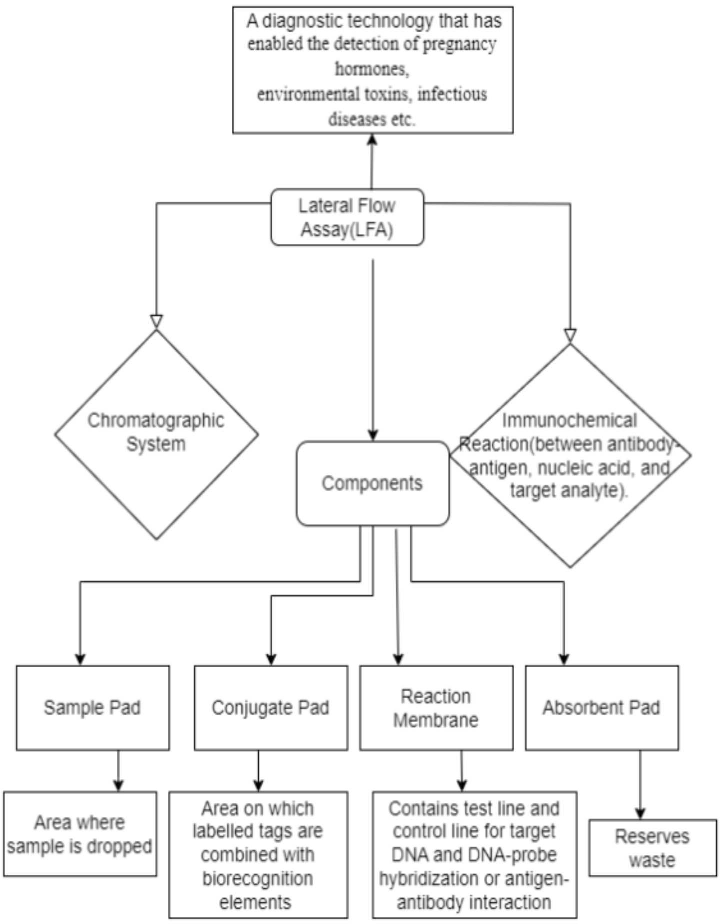

Figure 3. Structure and functions of a lateral flow assay

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necessitates an efficient, reproducible way to accommodate large-scale complex, and high-throughput device construction. An automated robotic liquid handling system is a novel development platform centered on flexibility and speed. The system comprising LFA is made of specific hardware and software that are able to do large experiments with discrete and continuous variables [43].

A very significant problem when establishing a laboratory with the latest technologies and automation is the cost barrier. Among the most recent ALHS currently available in the market, Tecan Fluent 780 costs about 110,000 € for the brand new version whereas a pre-owned version of Hamilton Microlab STAR costs about 50,000 €. The calculated expenses of establishing a complete laboratory line are estimated to be around 1 million € while the expenditure for installing independent liquid-handling systems can range from 10k to 300k €, excluding maintenance costs [44]. One way that it is reduced is by providing a multi-device platform.[12] These platforms encompass multitudinous devices that are able to work independently, but at the same time are able to integrate seamlessly with one another. The ability to provide separate functions and different courses of action outside of a single workstation allows the liquid handler to have more space for liquid operations, with large storage in an upright position providing a small footprint for the complete working area.[12]

Another way to reduce equipment costs is by utilizing a single equipment with limitations, which could then be enhanced with add-on modules that can be attached to the main worktable [12]. These add-ons are similar to those typically found in most advanced technical devices; this means that can facilitate greater access to automation for more users, especially those with fewer resources, but it might come with the disadvantage of lacking intuitive and powerful software [12].

Among other challenges, evaporation control remains one of the more serious concerns when working with automated liquid handling systems [07]. When large volumes are processed, evaporation may not be a significant problem. However, at the minuscule level, it becomes a serious issue. The evaporation rate in micro compartments can be decreased using handlers of various shapes [45]. This is the most common method in laboratories to prevent the edge effect of microplates, which is often caused by evaporation in the outer wells of the plate. However, the most precise results are received when using advanced sensors with a high sensitivity rating. A novel method includes a cover for crystallization plates. Such an innovation can lessen evaporation while simultaneously providing access to individual experiments.[46] However the design and development of a universal automatic seal-removing module or process is required for a high-automation dispensing technology.

Automatic handling of highly viscous biomaterials at the nanoscale volumes is practically challenging, but it is a crucial task in many biological research. Viscous materials can adhere to the walls of the container or the tool, so the droplet release takes more time [47]. The OSU researchers performed various types of research to discover the control factors for automatic contact dispensing of highly viscous materials at the nanoliter scale [48]. Their findings suggest that the most important factor is the dispensing distance (i.e., the height of the dispensing needle tip above the base of the well). If the distance is too large, the bio sample emerging from the needle can form a continuous tube that is not delivered to the well. If the distance is not significant enough, the sample can bollix up and adhere to the needle. Although a mathematical model exists to guide the liquid handling procedure,[49] methods for non-contact dispensing in this regard are still unavailable in the market. This is because piezoelectric or acoustic handling devices may not be capable of providing enough driving force to overcome the high

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viscosity, whereas solenoid-based products have a high risk of mechanical failure. Automatic liquid refilling and flowing for viscous liquids in the tube require extra-large driving forces to be used to draw in and out the liquid, an activity that still requires the development of a new method or mechanism [07].
There are several other challenges that are faced, the further we advance in the field. Clogging is a regularly faced problem in the inkjet industry. Dusty and viscous material, particles, or the accumulation of liquid debris may cause clogging in tubes, valves, and dispensing heads. Many procedures such as those transferring liquid or adding and removing equipment can lead to the formation of air bubbles. The bubbles can absorb some of the driving pressure, negatively affecting the dispensing performance, and causing errors. The current detection methods of clogging and air bubbles are based on sensors. A traditional method is to use ultrasonic cleaning after each use. Over the duration, ultrasonic cleaning damages the dispensing head. As such, new nondestructive, effective, and feasible solutions are required for this problem. Along with these, systems integration, that is the joining of different components of a liquid handling technology both hardware and software optimally is still a difficult task. Consequently, researchers are bound to choose between flexibility and very high throughput [07].

Clinical Workflow

Liquid Handling Devices (LHD) enhance the quality of experiments by performing more experiments at designated times and making operations more efficient against external factors and events such as the COVID-19 pandemic.[12] With Automated Liquid Handling Systems on the rise, developments have been made to advance operations in laboratory settings with the objective of supporting individuals with disabilities who may take up more time in the laboratory, as well as enhancing experimentation and research.
In genomic and proteomic applications, automated liquid handling systems assist and play a pivotal role in DNA/RNA extraction, protein purification, DNA/RNA purification, protein crystallization, DNA sequencing, protein expressing, DNA/PCR isolation, cell-based arrays, DNA extraction, peptide binding assays, gene expressing, protein arrays, genotyping, and antibody assays. With the help of these applications, cures for diseases would be found, and the structure, function, identification, and quantification of total proteins present in organisms, cells, and tissue would also be studied in depth and at length [07].
Automated Liquid handling systems also assist with liquid manipulation (dilutions, mixing, inoculations, and sample preparation gene sequencing, protein crystallization, drug screening, nucleic acid preparation, liquid biopsies, PCR setup which are millions to billions of copies of a segment of DNA, bio array workstations, next generation sequencing which is a sequencing technology used to detect the order of nucleotides in targeted regions or entire genomes of DNA and RNA, liquid-liquid extraction to remove pollutants from an aqueous mixture, enzyme-linked immunosorbent assay which helps quantify the amount of substance in a solution, solid phase extraction to help purify samples for analysis, and antibody testing, etc which can be performed easily with the use of LHDS), labware movement, and sample acquisition. In doing so, automated liquid handling systems make use of efficient time management, keeping things more organized, and getting practical results in a rapid manner [12].
Common applications for liquid handling devices include omics analyses of molecular profiles of organisms, large sample processing, processing of sensitive and forensic 395 samples usually involved

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in sensitive crimes for forensic profiling, evaluation of clinical samples, and integration of microscopic imaging which come useful for research and experimental purposes. Furthermore, Liquid Handling Devices are linked with highly analytical and rapidly processed equipment such as High-performance liquid chromatography (HPLC) for high-speed analyses. By doing so, liquid automated systems allow high-performance liquid chromatography to confirm and identify drugs, provide results that are measurable in quantity, and to monitor the progress of a disease in a period of given time [12]. By trading more human-centered tasks to automated or robotic liquid-handling platforms, time is set aside to be dedicated to experimental design, analysis, and interpretation of the results viewed through applications.

These automated platforms can also be useful in times of crisis and isolation such as the COVID-19 pandemic. These systems would help continue experimental work while minimizing human interaction and the spread of the global pandemic. By doing so, the research could be continued globally without reason for any external health issues to arise and to ensure that no work is being affected or delayed in any way. Liquid Handling Devices range from simple to complex machines but can all be categorized as robotic equipment with the ability to perform tasks in a pre-programmed fashion with varying levels of automation. For example, one type of Liquid Handling Device is a state-of-the-art device which is equipment that can perform multiple tasks within the same device such as liquid handling, labware movement, labware storage, protein/DNA purification, heating/cooling capabilities, sample analysis, etc. Another type of LHD is a multi-device platform that can perform a single task but can be connected to other single-purpose devices to perform more complex workflows. The last type of LHD are modular devices that are mostly concentrated in performing liquid movements, but they can include pieces of equipment that can be added to the main worktable such as heating/cooling devices, magnetic separators, or thermocyclers also known as PCR machines. There are various devices that are presently being utilized by various institutions. Freedom EVO, a device for sample preparation for deep sequencing, is used to demonstrate scheduling complications and solutions for an automated laboratory by the Nara Institute of Science and Technology, RIKEN Center for Biosystems Dynamics Research, and the University of Tsukuba. It is just one of the many devices that have gained extreme popularity in institutions and research papers in the past decade [12]. Mixing in microfluidics proposes a challenge due to laminar flows in microchannels. Passive mixers are difficult to control externally [50]. It has been found experimentally that automated mixing techniques yield better results than standardized manual methods. [51]. We draw the conclusion that automated liquid handling methods have been extensively applied to various biotechnological fields and have provided significant betterment and quality assurance.

Conclusion

Outdated manual processes can easily be replaced by more efficient automated methods because of their reduced errors, increased flow rate, limited time wastage, and minimized human supervision [07]. These automated methods also support individuals with disabilities through accessible tools given to efficiently manage their time in the laboratory. Furthermore, automated systems would also be useful in times of crisis such as the COVID-19 pandemic [12]. These systems would help continue experimental work while minimizing human interaction and the spread of an intercontinental pandemic. However, automated systems can be challenging to gain access to, especially in developing countries or in places where high-tech systems may not be easily accessible. It is to be mentioned that this research does not consider the market demands of LHD in developing countries. Further research needs to be done to compare the cost-effectiveness of using ALHS in small-scale and large-scale laboratories of low-income countries. Liquid Handling Devices need to be implemented further into more real-life applications and be further tested in all types of settings through regulation and integration during the design phase. In the upcoming future, automated liquid handling devices show great potential to make scientific breakthroughs and to integrate into various scientific environments as they are made more accessible and further introduced in new applications.

Author contributions

AM, HS, IIK, JD, ZT: writing- original draft, writing- reviewing and editing.

Competing financial interests

The authors declare no competing financial interests.

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