A review on robotics in life science automation

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***Abstract*— Automation is gaining importance in life science laboratories, where special robots are increasingly applied for tasks such as liquid handling and sample transportation. Robots play an important role in achieving the vision of the laboratory of the future, where automated devices are integrated into a continuous process and the need for human intervention is minimized. This paper provides an overview on the technological concepts that are already commonly applied for laboratory automation, and furthermore gives an outlook on novel technologies, such as mobile manipulators.**

Keywords—Laboratory automation, robotics, life science engineering, laboratory transportation

I. INTRODUCTION

Automation's gaining importance in the industry started from the manufacturing sector but is recently reaching a broadening spectrum of application areas ranging from smart homes and self-driving cars to service- and medical robotics [1]. The benefits automation brings vary from sector to sector, but in general it aims to raise productivity, to ensure constant quality and to free humans from repetitive tasks.

Automation in biotechnological and pharmaceutical research is already relatively common, especially for high throughput (HTP) applications, where a huge number of samples are processed. For this purpose, automatic pipetting robots, so-called liquid handlers, are commonly utilized, which can be considered a relatively mature technology.

In general, laboratory automation covers devices, processes or software that minimize the need for human intervention. The spectrum ranges from automated units, such as liquid handlers, centrifuges and readers, through means of sample management, such as storage carousels, robots and conveyors all the way to software for workflow creation, device control and data collection. The sector is estimated to expand globally from US$ 4.3 Billion in 2017 to US$ 5.9 Billion by 2023 by a CAGR of around 5% [2] and is considered to be an important application area for novel technologies of automation, mechatronics and robotics.

II. PROBLEM DESCRIPTION

Pharmaceutical sciences are one of the sectors that could benefit from utilizing automation technologies in their laboratories. Automation and robotization is inevitable, especially in laboratories where samples are processed in high amounts, such as in the HTP laboratory of the Takeda Pharmaceutical company. In the first part, this paper gives an overview on the technologies that are already applied for this purpose, such as robots for liquid handling and sample transportation. In the second part, novel technologies, such as mobile robotics were also considered, as means of bringing more flexibility to automated laboratory systems.

III. MARKET REVIEW

A. Laboratory robotics in Europe

A report for the European Laboratory Research & Innovation Group summarizes the status and prospects of laboratory robotics within the Horizon 2020 program [3]. This review is used as the backbone of the present section, because it provides an excellent overview on the present and future of laboratory robotics. Practical examples from the HTP laboratory of Takeda are also shortly introduced, which are then discussed in detail in the following sections.

In their report, the authors estimate the laboratory robotics sector to be worth between €2-3 billion and they describe it to be dominated by European suppliers. From the fields of application, pharmaceutical product development was identified as one of the most significant ones. There, laboratory robotics is already present in high-throughput screenings and in other laboratory processes that operate with high amounts of samples and require high repeatability. Such screening processes include procedures such as sample preparation, chromatography and optical reading, where small amounts of liquids are transferred into carriers and are processed in multiple steps. Since samples can be of various states of matter and of different forms, manipulators must have a wide variety of configurations. Although the most common way of processing samples is using multi-well plates (microtiter plates) with 96, 386 or more wells holding microliters to milliliters of liquids, other types of carriers, such as tubes, vials, cuvettes, flasks and bottles are also frequently used. Many manufacturers offer modular configuration options for their laboratory robots along with dedicated consumables and reagent kits. This approach enables a business model strategy, where supplies of such consumables, optional hardware and software upgrades, as well as service offerings can represent a significant contribution for gaining revenue in addition to selling the devices themselves.

In the above-mentioned paper, compact XYZ gantry robots are described to be the most commonly used type, which are usually equipped with liquid handling- and plate manipulating arms. Fig. 1 shows a liquid handler of type Tecan EVO (EVO) robot, which has two arms for plate manipulation, as well as an eight-channel pipetting arm. In the HTP laboratory of Takeda, five units of this type are in operation – although, with different configurations.

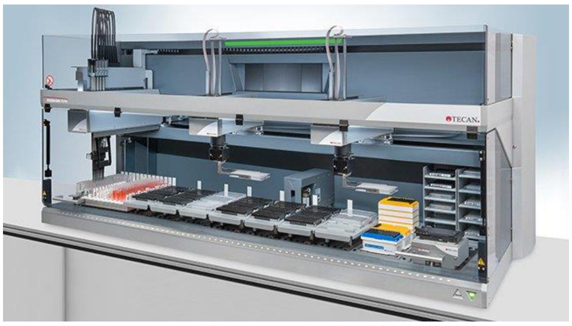

Fig. 1: Tecan Freedom EVO 200 liquid handler [4]

As means of sample transportation, articulated robots and Selective Compliance Assembly Robot Arms (SCARAs) are also referenced by the authors, along with compact table-top plate stacking mechanisms. For Takeda, a specialist company designed a similar robotic plate transportation system, which utilizes a SCARA and a conveyor to transport plates between the devices.

Also in the above-mentioned paper, mobile robotics is described as an emerging sector within laboratory robotics, providing a possible solution for implementing transport between automated islands and stand-alone devices. Examples, such as blood delivery applications in hospitals, and various research projects are mentioned including LISA from Fraunhofer IFF and the Adept Lynx.

As a barrier of the development, the users' lack of complex skills is identified, as well as the industry's fragmentation, which induces a lack of shared standards. However, a huge innovation potential is identified to lie in new technologies. These include miniaturized electro-mechanical solutions, 3D perception to manipulate complex solids, artificial intelligence to implement robotic laboratory assistants, co-bot systems and, ultimately, a deeper level of integration covering the whole workflow. Challenges are also identified, such as motion planning for robot arms considering the orientation and acceleration to avoid liquid spillage.

B. Turnkey robotic solutions for plate transportation

The first company that has been contacted by Takeda in connection with the automatic plate transportation system is the US-based Biosero. The company suggested that the EVOs be placed on custom-made frames, which would additionally house the two rails for the two SCARAs as well as the conveyor system under the table's surface. The chosen robot arms were identified as the so-called Precise Flex, the supplier of which proved to be Precise Automation (See section D).

A highly similar concept was provided by the Netherlands-based company Lab Services, which also utilizes the same type of robots, a custom-built frame and a similar conveyor (See Fig. 2).

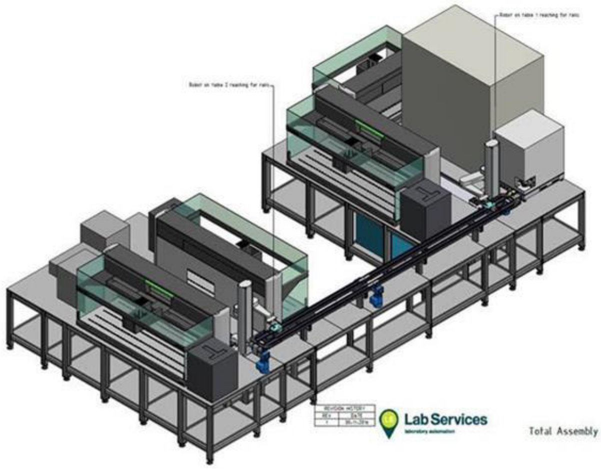

Fig. 2: Concept from Lab Services [5]

C. Further laboratory automation companies

Several other companies were identified that are active in the laboratory automation sector and that provide similar solutions to the ones described above. One example is the Swiss Aurovis AG, which specializes in AUtomation, RObotics and VIsion Systems – hence the name. The company is a distributor among other brands of Precise Automation, which is the manufacturer of laboratory robots, as well as of Tolomatic, which is a producer of motion solutions ranging from gearboxes and brakes to pneumatic actuators and complete electrical linear motion systems [6]. Aurovis offers engineering services and customized solutions based on the components it distributes.

The USA-based company HighRes Biosolutions also provides life science automation solutions, namely in the form of a modular system that consists of robot cells, docking stations and mobile modules (See Fig. 3). In their product range, a SCARA named ACell is listed, which has the same design and specification as the PreciseFlex from Precise Automation (see section D).

Fig. 3: HighRes Bio's modular laboratory automation solution [7]

The company's scheduling software, named Cellario, is capable of integrating with Laboratory Information Management Systems, provides an interface to create workflows and processes, and has various device drivers, including the support of Tecan EVO liquid handlers [8].

Agilent Technologies, provide laboratory instruments, services, consumables and applications, one of their most important markets being pharmaceutics [9]. The company's laboratory automation solutions include the software Vworks Automation Control, which has similar functionality as Cellario from HighRes Bio. Device drivers also cover the Tecan EVO and the company's own tabletop SCARA, BenchBot [10]. Complex automated workstations, such as the company's own BioCel [11], are controlled by the so-called Automation Control Unit, which can interface with various devices from Agilent and from other manufacturers.

The UK-based company Peak Analysis & Automation – PAA provides complete design-and-build service in laboratory automation for clients from the pharmaceutical and biotechnology industries, including Takeda [12]. Its control and scheduling software, Overlord™, is capable of controlling various third-party instruments, such as the Tecan EVO, as well as the company's own robots, which range from SCARAs designed for tabletop operation to larger variants designed for OEM applications.

D. *Components of a sample transportation system*

1) *Robot arms*

For handling microplates, robot arms provide flexibility by being able to reach diverse devices organized along a line or a circle. Fig. 4 shows a comparison by Precise Automation, between a circle pattern for a six-axis robot and a linear pattern for a rail-mounted SCARA. The latter, the PreciseFlex arm – or variants of it –, occurs in the product range of multiple system integrator companies, as seen inFig. 5.

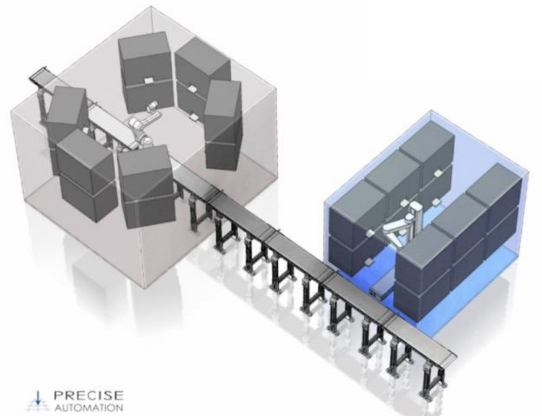

Fig. 4: Precise Automation's comparison of robot layouts [13]

The PreciseFlex arm has collaborative features, such as hand-driven teaching possibility and cage-free operation, thanks to collision force limitation in accordance with the ISO/TS 15066 Standard on Collaborative Robots. The four-axis SCARA is available in various sizes, as summarized in Table 1. The robot's interfaces range from RS-232 through Ethernet to an E-stop input alongside with 12 digital inputs and 8 digital outputs. Various methods are available for the programming and operation, such as a web-based interface, advanced programming interfaces and PC control using the TCP/IP Command Server [13].

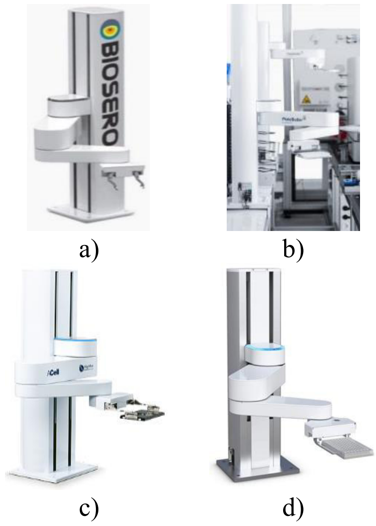

Fig. 5: Table-top SCARA solutions from various companies

a) PreciseFlex from Biosero [16]; b) PlateButler from Lab Services [17];

c) ACel from HighRes Bio [8]; d) Benchbot from Agilent [11]

Dimension	**Options**
Linear Z-Axis length	400 mm or 750 mm
Maximum reach	576 mm or 731 mm
Linear rail length	1 m, 1,5 m or 2 m

Table 1: Dimension options for the PreciseFlex robot

Alternative to SCARAs, articulated robots with four to seven joints could be applied. For them, similar linear extensions are also available referred to as a seventh axis. Vention and Rollon S.p.A. are two companies that provide seventh axis solutions for arms from Universal Robots. These systems are, however, optimized for industrial applications, their dimensions being too large for laboratory automation purposes [14], [15].

2) *Grippers*

In a laboratory, a robot may have to transport various types of objects, such as microplates, tubes and bottles. These objects are different in size, and because of that, a different gripping width is needed for each of them. Plate transporting robots, such as the liquid handling arms of the EVOs, or the PreciseFlex are often equipped with a gripper that is not capable of closing all the way, but only to a with, which is appropriate for gripping plates either in the landscape or in the portrait format. Universal grippers, such as the RobotiQ 2F series [16] on the other hand are capable of closing all the way, which enable gripping thin objects. However, to retain the gripper's ability to grip wider objects, such as plates, a wider variant is needed, which increases the weight and the costs. To overcome this, one possible solution is to use custom-made fingers that have multiple gripping points for different kinds of objects, such as on the robot used in Fraunhofer's AUTOSTEM setup [17].

Fig. 6: Multi-gripper from Fraunhofer [17]

The use of automatic tool changers (ATC) would also be a possible solution. Although, making the whole gripper automatically interchangeable requires a complex interface, which provides both mechanical and electrical connection. Instead of this, Tecan implemented a finger swapper mechanism for its Fluent series liquid handlers [18].

3) Conveyors

In many laboratories, the devices cannot be reached by one robot arm on a single rail, but an additional conveyor system is required to transport the microplates between multiple robot arms, serving as the backbone of the system. In the case of Takeda's laboratory, the linear conveyor will be located along the wall and will be approximately 4 m in length. The transportation task requires one or more carriers that travel between the two end positions, where the robots can place or pick up the plates.

A magnetic conveyor system similar to MagneMotion's Magnemover Lite was identified to be integrated in the concept of Biosero (See section B). The system, which is recommended among other fields for laboratory automation, consists of modular motorized track segments, which can be combined into various configurations.

IV. Literature review

After reviewing the commonly available laboratory robotics solutions, this section discusses some novel technologies that are subject to academic and industry research.

A. Academic research regarding laboratory robotics

The Center for Life Science Automation (CELISCA) is an institute of the Rostock University, which is specialized in topics that highly overlap with the context of this paper. Because of this, several research projects of the institute were reviewed, and are summarized in this section.

Laboratory automation could not be achieved without the appropriate software to control and monitor the processes and workflows. Li et al. present a 4D simulation system that integrates a Process Control Software (PCS), a Data Management System (DMS) and 3D animations [19]. Laboratory Information Management Systems (LIMS) are essential tools of laboratory automation for tasks such as data processing, workflow management, resource planning, sample management, quality control and instrument integration. Blazek et al. [20] provide a comparative evaluation of open source LIMS software in the context of academic research. The ability to access and change the code of the software ultimately brings the possibility of customizability, but security vulnerabilities may occur thanks to custom scripts and plugins not being kept constantly up-to-date.

Xianghua et al. survey the integration possibilities of laboratory equipment [21]. The study provides methods to use robot arms to manipulate laboratory devices that are not designed for automation, but for human operation, as seen in Fig. 7. In their paper, both aspects for mechanical interfaces and aspects for software interfaces are discussed. For the latter, workarounds, such as UI-manipulation with mouse- and keyboard emulation and optical character recognition (OCR) were used.

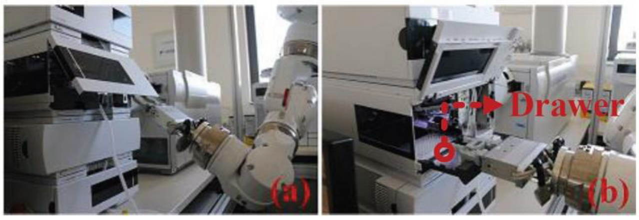

Fig. 7: Manipulating laboratory equipment with robot arm [21]

Robots in a laboratory are expected to work alongside humans in a collaborative manner, and to achieve this, safety is a critical aspect. Kirschner et al. provide a list of relevant parameters of sensitive collaborative robots from various manufacturers such as ABB, KUKA and UR [22]. The authors conclude, that the specified maximal collision force of a robot is only valid for certain velocities, thus they recommend evaluating every hazardous situation, when applying a collaborative robot. The safety of collaborative mobile robots depends on even more factors. Kim et al. [23] discuss service robotics and review the related ISO standard (ISO 13482) in the aspect of Protective Stop Space and Safeguarded Space. They present a method to determine the radii of these areas taking the robot's braking performance, the relative velocity as well as a perceived safety into account.

In CELISCA, besides stationary robot arms, mobile robots are also utilized, mainly for transporting various labware between workstations, rooms and even between floors [24]. In this application, a four-layer control system is responsible for assigning tasks to the specific robots, calculating paths and executing the task, while the navigation of the robots is implemented with ceiling landmarks and a StarGazer camera system [25].

Liu et al. [26] discuss the control system, the door control and a robot-human interaction proposing an XML-based command structure as well as a multi-robot communication architecture. The mobile robots at CELISCA are also capable of navigating to their charging stations when necessary. Thurow et al. [27] discuss a waypoint-based navigation method in the facility throughout multiple floors. This task requires the robots to operate the elevators and automatic doors as well. A concept for the grasping of lab ware with the help of a Kinect-sensor is also presented. Lab ware manipulation is discussed in detail by Ali et al. [28]. In their concept, the Speeded-Up Robust Features (SURF) algorithm was used for the recognition, and multiple grippers were designed.

A compact mobile manipulator is under development by the Fraunhofer Institute for Manufacturing Engineering and Automation IPA under the name Kevin [29]. The idea behind this concept was to transport microplates between different laboratory workstations autonomously, while retaining flexibility and the ability to move arbitrarily. For this purpose, the mobile robot base Care-o-Bot 4 was equipped with a PreciseFlex SCARA, which can grip standard microtiter plates. The base is an omnidirectional mobile platform equipped with laser scanners and is capable of autonomous navigation. Similarly to most mobile platforms, the positioning accuracy of the base alone is insufficient for grasping plates with an indicated value of 2-3 cm. To overcome this, a camera system and optical markers were used to detect the position of the carriers relative to the robot. Since both the base and the SCARA are commonly used in environments shared with humans and are certified, the combined mobile manipulator is also suitable for collaborative operation.

B. Industry research

Laboratory automation companies, such as the ones introduced in chapter III also started to experiment with mobile manipulators for transportation applications. Biosero, for example developed a system consisting of a mobile base of type Omron LD, a PreciseFlex SCARA and a Cognex industrial camera [30]. The concept highly resembles the one of the Fraunhofer Institute, but Biosero's robot can also be controlled by the company's scheduler software, Green Button GO™.

V. Conclusion

Robots are gaining more and more importance in laboratory automation applications. Gantry robots are commonly used for liquid handling tasks, while SCARAs and articulated robots are often utilized for handling objects, such as microplates, tubes and other labware. In many applications, the robot arms are mounted on linear rails to expand their working area. However, to achieve the vision of the laboratory of the future, where the whole laboratory process is automated in a continuous manner, and human workload is minimized, connecting the separate stations is also necessary. The application of mobile manipulators for solving this problem represents a promising field of research; however, it brings challenges such as finding a solutions for the platforms' insufficient accuracy, and for a collaborative operation.

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