

Automating Laboratory Processes by Connecting Biotech and Robotic Devices

¹Rajesh Kumar Sahu ²Prasant Jaiswal ³Jaydev Mandal ⁴Saroj Kumar Rout
Gandhi Institute For Technology, Bhubaneswar

Abstract: The constantly growing interest and range of applications of advanced cell, gene and regenerative therapies raise the need for efficient production of biological material and novel treatment technologies. Many of the production and manipulation processes of such materials are still manual and, therefore, need to be transferred to a fully automated execution. Developers of such systems face several challenges, one of which is mechanical and communication interfaces in biotechnological devices. In the present state, many devices are still designed for manual use and rarely provide a connection to external software for receiving commands and sending data. However, a trend towards automation on the device market is clearly visible, and the communication protocol, Open Platform Communications Data Access (OPC DA), seems to become established as a standard in biotech devices. A rising number of vendors offer software for device control and automated processing, some of which even allow the integration of devices from multiple manufacturers. The high, application-specific need in functionalities, flexibility and adaptivity makes it difficult to find the best solution and, in many cases, leads to the creation of new custom-designed software. This report shall give an overview of existing technologies, devices and software for laboratory automation of biotechnological processes. Furthermore, it presents an outlook for possible future developments and standardizations.

Keywords: laboratory processes automation; data communication; robotic production; device integration

1. Introduction

Biotechnological products play an ever-increasing role for several sectors of the producing industry. In the medical sector, some of such processes are already established (e.g., insulin production), and also the pharma industry takes more and more advantage of biotechnology (e.g., CAR-T therapies). In food production, gene-modified plants promise higher yield using less pesticides. In a few years, meat grown in the laboratory may be found in grocery stores [1]. Another novel sector is that of synthetic biology, where biological products and their gene codes are fully engineered to create food, medicine or even replacements for technical parts [2].

Consequently, biotechnological production needs to become more cost-efficient, resilient, robust, reliable, and affordable for the greater population and be steadfast against competitive products on the market. Therefore, production processes must follow the development of other industry sectors, such as automotive, microelectronic or chemical, and change from partly or purely manual production steps to full automation.

The advantages of the transformation go beyond lower production costs and a higher yield. As labor steps, as well as measurements and decisions made by machines, are

far more repetitive than those of humans, a far steadier product quality can be reached as well as more thorough and reliable production, measurement data acquisition and documentation. Human errors are eliminated, and employers do not need to be trained any more on complex production steps. Companies can focus their personal resources on development, testing and maintenance rather than production [3,4].

Hence, it is not surprising, that several biotechnological companies and institutes are already examining the transfer from manual to automated production. A growing number of manufacturers offer automated solutions for biological processes or process steps or devices that can be connected into an automated environment. Furthermore, a steady increase in publications being related to robotics or automation can be observed, showing the rising interest of research institutes in that topic [5,6].

The downsides to the mentioned advantages are the challenges that institutes and companies face during their change from manual to automated production. Those lie not only in the transfer of manual to automated production but also in meeting the high regulatory requirements of biotechnological production.

2. Automation

In manufacturing, automation is defined as the technology by which a procedure is executed without human assistance. Humans may be involved as observers or participants, but the process itself is self-directed [7]. In a system, a (production) process is determined as a set of interacting operations by which matter, energy or information is transformed, transported or stored. Separable operations can be grouped to form logical or functional sub-processes. Accordingly, the degree of automation of a system is specified as the ratio of already automated operations to the total number of all operations of a system [8].

Based on the latter definition, automation can be seen as a continuum of automation levels. The scale ranges from the lowest level of fully manual where every operation of the overall process is performed manually by a human operator to the highest level of full automation where every operation is executed without human involvement. Thereby excluded are switch-on and switch-off actions, the specification of desired values or an intervention in case of malfunction. Accordingly, Frohm et al. propose seven levels of automation for mechanical devices where zero equals "totally manual" and seven "totally automatic" [8,9].

In biotechnology, the constantly growing range of applications of advanced cell, gene and regenerative therapies raises the need for an efficient production of biological material and novel treatment technologies. To meet the increasing demand for biomedical products in the long term, manufacturers and researchers raise the level of automation in their laboratories. The degree of automation in biotechnology is low in comparison to classic production sectors such as the automotive industry. One reason is the requirements of biotechnological products in terms of process flexibility, individual production and sterility, while the other is the high regulatory demands to ensure a safe and reliable application of the product [10]. Especially in high-wage countries, automation has been a key factor to lower production costs and higher throughput. In addition to the typical goals of automation, it provides further advantages such as an enhanced reproducibility, reliability and improved work safety when handling dangerous reagents. Furthermore, automation leads to a faster translation from research to usage in a clinical setting [5,11].

A conventional biological laboratory mainly has equipment that belongs to automation level five, i.e., a static workstation designed for a specific task such as a centrifuge, polymerase chain reaction (PCR) thermocycler or spectrophotometer [5]. In the biotechnical sector, examples of systems with an automation level of seven are fully automated plants producing cell cultures such as the StemCellFactory [12] and StemCellDiscovery [13]. These systems use a robotic arm mounted on a linear axis, which autonomously navigates between experimental benchtop stations performing reagent-dispensing and handling operations. To further increase the level of automation in a biological laboratory, either existing equipment must be interconnected physically or in software or new devices, which are

capable of more complex tasks, have to be acquired [5]. One resulting technical challenge is to connect a heterogeneity of complex operations and device interfaces. Furthermore, a large number of different equipment suppliers and a low level of standardization in terms

of software and materials such as labware and consumables complicate the problem [5,14].

In addition, the production of biomedical products has to follow a strict regulatory framework. In biotechnology, good manufacturing practice (GMP) contains the most important regulations, which defines high standards for the sterility, purity and function of the end product as well as the used process and analytic devices [15]. One part of GMP that is especially important for automation in biotechnology is good automated manufacturing practice (GAMP), which sets further requirements onto software design, including efficient, error-free and well-tested source codes and programs as well as comprehensible, reliable and safe data storage [16]. Therefore, this must be taken into account during the design and construction of the plant, the procurement of devices and materials and the creation of software [17].

3. Basic Requirements for Automation

In this section, the basic requirements for automating a laboratory process that is so far performed manually are presented. These prerequisites address the equipment used during the execution of the protocol, the physical and software interfaces that depend on it, material transport, and the need for control software [4,14,17]. If automation was not considered during the early stages of the development cycle, these requirements represent major challenges for the operator [4].

Many factors need to be considered when automating a standard operating procedure (SOP). On the one hand, the overall process must be separable into modular steps that can be applicable to technical devices [10]. On the other hand, the SOP has to be automatable regarding handling of materials and containers. Therefore, a key aspect is the amount of product that will be produced by the process. The suitability of all equipment and containers depends on the desired output quantity. To avoid bottlenecks and reduce the variance in container sizes, all process steps should be dimensioned to process input materials in a similar range of quantity [17]. Furthermore, all operations must be determined with quantitative values. Information such as “shake carefully” or “add a little fluid” cannot be handled by machines and needs to be specified. In addition, many process steps depend on qualitative measurement values such as the evaluation of optical observations such as cell shape, medium color, confluence or transparency. Due to the error-proneness of manual measurements and human-induced variability, these evaluations should be performed automatically. This can be accomplished by artificial-intelligence-based algorithms for image recognition, as has been shown in several studies [11,13,18].

To fully automate an SOP, various devices need to be integrated into a production plant. These individual components automatically execute a specific function or sub-process. For different devices to interact with each other, basic requirements for physical as well as software interfaces must be met [10,14].

Considering the physical system, all relevant sites of the device such as the material intake or storages must be physically accessible. Accordingly, unobstructed access is necessary to easily place, insert or remove objects and other media [7]. Performing these tasks manually is often not a problem for a human being. However, a robot is less flexible and requires more space for its movements. Therefore, a device must provide enough space for robotic operations and needs, for example, motorized lids or caps that can be opened by an external robot.

To integrate a device into a software system, it needs communication interfaces. These should be thoroughly documented, designed as open as possible and enable both control and monitoring of the hardware. Usually, a single central control software is used in a production plant. It sends control commands to the individual devices executing these commands. Through the feedback of the status values, measured data of analytical equipment and other data, all operations are recorded and monitored in a central unit [14].

Online monitoring of processes and integrated control are crucial tools to achieve GMP compliance. They enable the characterization and documentation of the process and its adaptations to process changes [17].

In a nutshell, the presented requirements for the automation of a laboratory process clearly show that manual SOPs usually have to be adapted for automation. Therefore, modeling a new process or adapting an existing one is an essential part of automation. First, the individual process steps and their dependencies are defined. Subsequently, all tools, equipment, media, materials and biological products are selected and process parameters, such as quantities, temperatures and sizes, are determined. Finally, the process model must be formalized in a way that it can be understood by both humans as well as machines. Due to the high complexity in laboratory processes automation, experience has shown to better adapt process and equipment and materials in multiple iterations [19].

4. Current State of the Art

As mentioned before, the devices being available on the market differ greatly between being fully compliant to automation and manual usage only. This is true for the mechanical interaction of robotic and biotechnological devices as well as the digital interface for sending commands and receiving data. Therefore, this chapter shall give an overview about existing solutions, examples for automation-readiness and possible workarounds.

4.1. Physical Interfaces

As described previously, the requirements for robotic opening and closing, loading and unloading of devices differ from those for manual use. While some devices on the market are “by coincidence” automation compatible, other manufacturers have put much thought into providing robotic availability. Additionally, a large group of devices can be found, that are not—or only with great effort—accessible by robots. The greatest challenge is posed by high space limitations for the robotic tools to move in as well as irregular, flexible or small surfaces for gripping a material.

4.1.1. Loading Devices

One of the automation-intended devices is the PCR device QTower3 Auto (Analytik Jena GmbH, Jena, Germany). PCR devices control genome duplication reactions by continuously heating up and cooling down the sample, mostly by using a heating plate that the sample plate is pressed into. Inserting and later removing the sample with force is difficult for robots and can result in the robot losing touch. The QTower3 Auto does not require such an insertion with force. It provides an opening drawer that moves out of the front of the device, thus offering much operating space for the robot. The sample plate is simply put onto the drawer. After it is retracted, the sample plate and heating block are connected inside of the device. Removing the sample is carried out in a similar fashion.

Another example is the microplate sealer ALPS3000 (ThermoFisher, Waltham, MA, USA). It takes sealing foil from a roll, cuts it into pieces and heat-attaches these onto the sample plates. The device provides a drawer with enough space for handling the plates with a robot. Hereby, no force is needed for putting or taking the material.

The centrifuge 4–16 KRL by Sigma (Sigma Laborzentrifugen, Osterode am Harz, Germany) has a strong shell for protection and heat-sealing with only a small opening on the top. For loading and unloading, the user needs to reach through the opening to place the sample into the device. This is problematic because a robot arm is usually thicker and less flexible than a human arm. Adapting the design of the robot's grippers solves this issue. Long grippers enable the robot to reach to the bottom of the centrifuge. However, they can be at a disadvantage when performing other operations in space-limited areas of the automated platform.

Another solution to this problem has been realized in the cooling storage for falcon-tubes, which is a custom-made device integrated in the automated platform StemCellDiscovery [13]. This device also controls its inside temperature for cooling the cell medium

and has temperature-isolated walls with only a small opening at the top. As this opening is too small for a robot gripper, the device has a lifting mechanism. The tubes are vertically moved through the opening where the robot can easily take them.

4.1.2. Handling Materials

Most disposables, such as flasks, bottles, tubes or plates, are rather made for human instead of robotic usage. While the basic geometry of most materials is standardized, the specific geometry and texture of surfaces at which to hold the materials are not. This is of no relevance for manual use. For robots, however, a variance of these can mean the difference between reliably holding and often losing touch. As robot grippers are far less flexible than human hands, they normally need to be specifically adapted to the materials they are supposed to handle. The more different disposable sizes the robot shall handle, the more complicated the design of its grippers will be. Therefore, already in the process design, attention should be paid to keeping the variety of different materials as low as possible and making sure that vessel sizes and geometries do not change, e.g., when they are obtained from another vendor [5,20].

Humans and robots have in common that they can handle large materials far more easily than small. The bigger a vessel, the more surface it provides for gripping and placing, reducing the impact of moving or positioning tolerances. Often, however, larger vessels do have larger tolerances in geometry, eliminating this advantage. Therefore, it is recommended to design a system moving as precise as possible and handling large tolerances.

The robot grippers of the automated cell production platform AUTOSTEM [21] have been designed to handle several geometries with just one pair of grippers. The platform is divided into two areas with different cleanroom grades, each of which contains a robot and uses specific set of materials. Therefore, also gripper designs need to be different and specifically adapted to the materials they are supposed to handle. Both grippers consist of pneumatic universal grippers from Schunk (PGN+80-2-SD, Schunk, Lauffen am Neckar, Germany) with attached custom-made gripper blades that have been shaped to handle all required materials (Figure 1). While the pneumatic drive provides stable and simple control, caution must be taken to avoid any tolerance to exceed the gripper stroke. As the gripping blades can only open by a certain distance, the positioning tolerance of the materials to grip must be inside that distance. Otherwise, the gripper will collide with the material instead of getting hold of it.

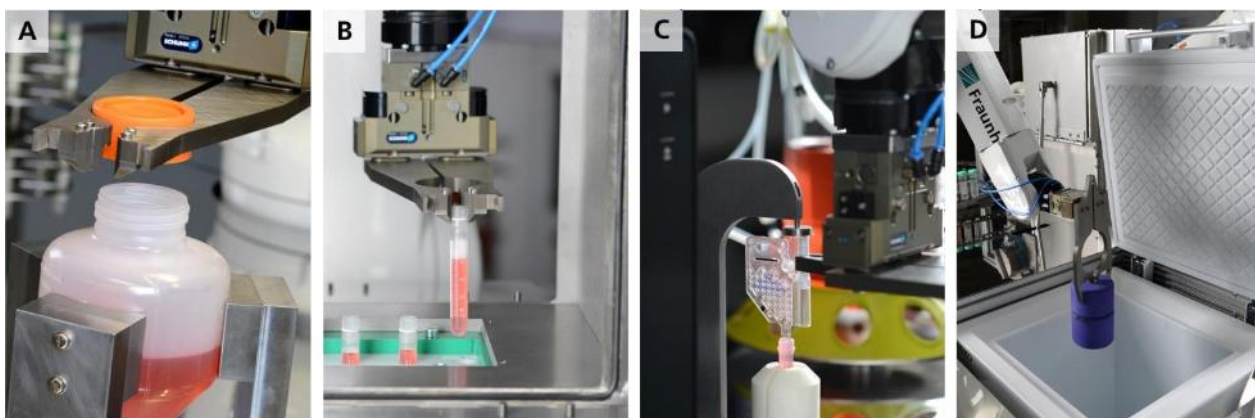


Figure 1. Gripping of different materials of the robots in the AUTOSTEM platform [21]. (A,B) show the robot in the sterile platform area while (C,D) show the other robot in the unsterile area.

A different approach has been realized for the robot of the platform StemCellDiscovery [13]. A servo gripper by PTM (SG-00014, P.T.M. Präzisionstechnik GmbH, Gröbenzell, Germany) is used, which also has attached custom-made gripper blades (Figure 2A). The

difference here is that due to the servo drive, the gripper stroke is much higher. Furthermore, the gripper can be moved into any position instead of just being fully open and fully closed. In addition, the grippers are force sensitive and thus can be set to close until they hold the material, independent of its size, and without gripping it with too high forces to risk damaging it. However, such a device is far more complicated to control and has a higher risk of failure.

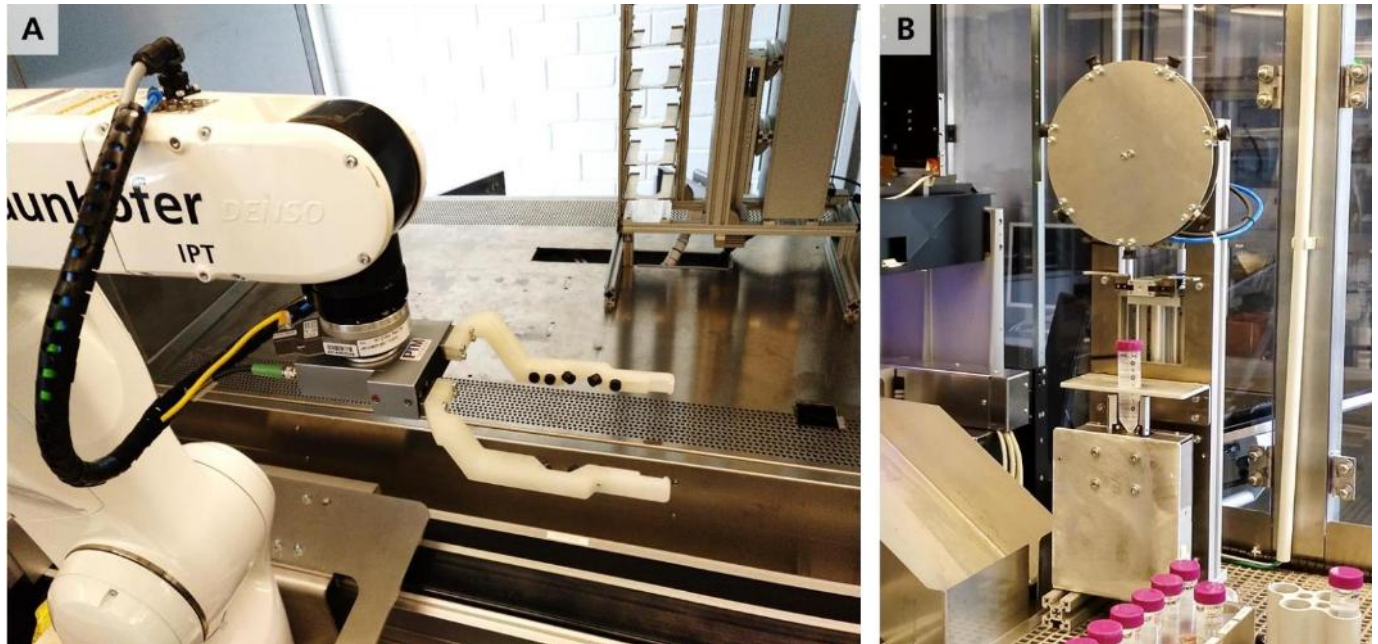


Figure 2. Devices in the StemCellDiscovery platform [13] with (A) the robot and its motor-driven gripper and (B) the decapper to automatically open and close screw caps.

Opening and closing vessels, which are intuitive and simple tasks for humans, also provide some challenges for robotic automation. While cell plates, for which the lid is laid onto, are trivial to handle, vessels with film hinges, especially when being small, require very complex solutions. Screw caps provide an air- and fluid-sealed closure and can be handled automatically with moderate effort. One solution is provided in the StemCellDiscovery [13]. The decapper consists of turnable grippers to spin the tube. The lid is meanwhile held by grippers that are mounted on a vertical rail. When the lid is being unscrewed and moves upwards, the gripper can follow. Once loosened, a vertical actor moves the gripper to suction cups at the top of the device. This way the lid can be held without its wet side touching any surface (Figure 2B).

4.2. Digital Communication Interfaces

While the automation of custom-developed devices is quite simple when using programmable logic controllers (PLC) or microcontrollers, great caution must be taken when obtaining devices that shall be integrated into the automated environment. Some devices, even though being highly modern, complex and technically advanced, do not allow for receiving commands or sending data via a digital interface. Other devices may allow only partial automation and either enable external software to activate some but not all the available functions, or the execution of digitally triggered commands still requires manual steps, e.g., pressing a start button. The devices that provide full bilateral digital communication offer different well implemented but unfortunately not yet standardized solutions.

The automated PCR device QTower3 Auto (Analytik Jena GmbH, Jena, Germany) is connected via USB to the host computer. The vendor provides a dynamic link library (DLL) file that can be included in the custom control program and provides libraries containing functions to send commands and receive data.

The incubator Cytomat 24C-IG (Thermo Fisher Scientific GmbH, Waltham, MA, USA) provides a serial RS-232 interface for digital communication. In the RS-232 standard, user data are sent as a time-series of bits defined by two voltage levels that correspond to logical one and logical zero. In most applications, the RS-232 interface is becoming less important because current standards, such as Ethernet or USB, enable higher transmission rates, support greater distances and are less vulnerable to interference. However, in laboratory automation, the interface is used because of its simplicity and ease of implementation [22]. In the case of the incubator, the vendor provides a communication datasheet with commands that can be implemented in the controlling software. This device connects with a DSUB-9 plug, and other devices have USB plugs that also run the RS-232 communication protocol.

The pipetting robot Microlab STAR (Hamilton Company, Reno, NV, USA) provides a USB connection that only connects to the vendor-specific software VENUS. Any external control software needs to communicate with this program via comma-separated value

(CSV) or Microsoft Excel files that are stored on and read from a server.

An interface that seems to establish itself as a standard in biotech devices is OPC DA.

The bioreactor controller in-Control (Applikon Biotechnology, Delft, The Netherlands) is using it for communication. The advantage of this interface is that the user can see the supported control functions via a corresponding OPC DA client. However, a communication datasheet from the vendor is necessary for the details to the function and the required parameters. For the communication, an OPC DA-Server is needed. In the case of the in-Control, that Server is provided by Applikon Biotechnology. Furthermore, a special client is needed that must be integrated in the controlling program for enabling it to communicate with the OPC DA-Server and must be obtained separately from corresponding software providers.

In recent years, the communication standard of other industry branches has already moved to the communication standard OPC Unified Architecture (OPC UA), which is more flexible, universally applicable and already a standard in other branches such as, e.g., the automotive sector. The development of biotechnological devices has a delay here, as manufacturers need to obey higher requirements when certifying their software, thus major changes, such as switching to another communication standard, require more effort and need a longer time. One device already implementing an OPC UA interface is the CTS Rotea Counterflow Centrifugation System (Thermo Fisher Scientific GmbH, Waltham, MA, USA). It is to be expected that more devices from that manufacturer and other manufacturers will follow in the next years.

Some devices can be connected to the manufacturer-specific controlling software but do not provide any interface to communicate with custom software. In this case, workarounds are possible. For example, the software can be installed on a separate computer. The custom controlling software can be set to handle that computer's mouse and thus set commands in the manufacturer's software. Of course, a readout of data from that software is only possible indirectly, by letting the manufacturer's software save the data in an external file that can be read by the custom software.

4.3. Control Software

In accordance with the rising trend of automation in biotechnology, a multitude of software for controlling automated devices has been developed by industrial companies and research groups. However, they differ greatly in terms of options for device control, process design, regulatory compliance and flexibility and adaptivity to communication interfaces. The following section shall present several concepts for automation control software in biotechnology by describing corresponding examples.

The Software eve (Infors AG, Bottmingen, Switzerland) is a flexible tool to control biotechnological devices. Once installed on a windows server, it is accessible via a browser of any operating system. It can communicate via several OPC protocols with devices from Infors as well as other devices being compatible. If they are not, Infors offer the development of custom communication interfaces. The user can define processes for each

The researchers at the Laboratory for Machine Tools and Production Engineering (WZL), RWTH Aachen University, have developed a similar solution with the automated cell production site, iCellFactory, including an own software to control the platform. This concept, however, has a high focus on platform flexibility; here, the position of the devices does not need to be defined and can be changed any time, because every platform possesses an individual data matrix code (DMC) that can be recognized by a camera to evaluate the exact device position [28]. Here, a software architecture consisting of several programs enables the flexible integration of devices from multiple manufacturers and with different interfaces [29], which can all then be integrated in programmable processes [30].

Industrial companies also provide such solutions. PTC Inc. (Boston, MA, USA) have developed the software ThingWorx that connects devices of different manufacturers for process automation [31]. A multilayer concept has been chosen to provide communication via several protocols that are realized with the software Kepware, which implements about 200 interfaces and works as a translator between ThingWorx and the platform devices. The software allows for defining processes, provides user logins and can be GMP certified, if certain criteria are met [32].

Table 1 shall provide a quick overview of the differently described software. It shows

- Which operating system the software can be installed onto;
- Which communication interfaces it can connect with;
- Whether it communicates only with devices from any or just a specific manufacturer;

	Eve (Infors)	Unicorn	BlueVIS4.0 (BlueSens)	Control Software (Fraunhofer IPT)	St iCellF: RWT
Operating system	all	Windows	Windows	Windows	W
Communication interfaces	OPC DA, OPC UA, OPC XML DA, custom adaptations possible	OPC DA	RS-232, RS-485, OPC DA, OPC UA, RTU, TCP, custom adaptions possible		OPC U adapti

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Whether it can send commands and read data, such as measurements or status information;

Whether it provides tools to analyze the read data;

Whether processes can be defined that include several devices, to be able to automate complete procedures that include several different processing steps;

Whether single users or user group logins can be defined to define user rights;

Whether every performed action is logged with time and, if available, operating user,

If the software can be obtained as GMP certified;

If the software itself can communicate with other external software, such as an overarching control system.

Table 1. Overview of different software for controlling automated biotechnological processes.

USB, Ethernet, OPC DA, OPC UA, RS-232, custom adapions possible						
Send Commands	yes	yes	yes	yes	yes	yes
Read data	yes	yes	yes	yes	yes	yes
Data analysis tools	yes	yes	yes	yes	no	yes
Define cross-device processes	no	no	no	yes	yes	yes
User logins	yes	yes	yes	yes	yes	yes
Action logging	yes	yes	yes	yes	yes	yes
GMP compliant	yes	yes	no	no	no	yes
Connection to external software	no	yes	yes	yes	no	yes

More and more manufacturers are adapting their existing devices or creating new versions that are suitable for an integration into a robotic automated environment. The mechanical requirements for robotic handling as well as data communication seem to be increasingly understood and implemented in new developments.

6. Conclusions

As automation of biotechnological laboratory processes is a young field compared to automation in other sectors and is just gaining relevance in today's industry, the implementation of such an automation is still challenging and requires thorough research and development. This includes a detailed definition of the manual process while assuring that each of the single process steps is transferrable into automation. The geometric limitations of robot grippers, decappers and storages require the lowest possible variance in shapes of flasks, tubes and plates, which, again, may affect process design. Thus, biological and technical experts need to work in close cooperation to create a process that is both fully transferable into automation and still yields the desired products and results, which, at the current state of the art, may not be possible for every process. Additionally, automated processes are more sensitive to changes. If, for example, the process is changed in a way that requires an additional tube size or storing materials at an additional certain temperature, extensive changes of the production platform may be necessary.

When researching for automation-suitable devices, profound expertise and experience in automation and robotic handling are mandatory. Some handling steps that are intuitive and simple to perform manually may be almost impossible to be copied by robots. Here, the choice of the best-fitting robot is just as important as that of devices and materials. If GMP compliance is of relevance, it must be assured that the certification is provided for the corresponding device. In most cases, additional custom developments are necessary, which can be specialized robot grippers or devices for automating certain process steps that are not available on the market.

In most cases, it is not possible to obtain all devices from the same manufacturer. As data communication standards, such as OPC DA, are spreading—though are still far from being accepted by the majority of manufacturers, and even the same manufacturer may implement different communication interfaces—flexibility in device communication is often unavoidable. For any communication protocol that shall be implemented, the required data flow needs to be defined beforehand, to be able to assure that it can be realized with the specific communication interface. The availability of device communication for the same device type can differ greatly among manufacturers. While some may provide it for free, others charge a huge additional price for software clients or adaptations, and some may not offer it at all. Therefore, a thorough definition of requirements and detailed communication with the manufacturer is recommended before the device is obtained.

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