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Review article

A review on the advances in non-application specific laboratory automation

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A R T I C L E I N F O

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A B S T R A C T

Automation is dominating industries with high-throughput processes. Recently automation began gradually to make its way into laboratories in the biochemical, biotechnological and pharmaceutical sectors. For laboratory employees and researchers, it is therefore difficult to keep an overview of the rapid progress of new technologies in this field. Often, they are only aware of the application specific solutions required in their environment. The aim of this work is to review advances of non-application specific laboratory automation in biochemical, analytical and biotechnological laboratories. An insight into the essential hardware and software infrastructure required for non-application specific laboratory automation is provided, and existing state-of-the-art hardware and software technologies are elaborated. Emphasis is placed on the plug-and-play functionality of the different technologies and missing links comprising internal mechanical and control interfaces. Existing approaches to holistic workflow automation are considered according to their hardware- and software implementation. To sum up, this review investigates the state of the art comprising software and hardware technologies for use in holistic workflow automation. We identify criteria that pave the way for future developments and areas with optimization potential to enable plug-and-play functionality and thus cost-effective and rapid integration benefiting end users.

1. Introduction

The level of automation in laboratories across the biochemical, biotechnological, and pharmaceutical industries is constantly advancing. Nowadays, it is hard to imagine a laboratory without automated equipment, from simple manual pipettes and balances to fully automated high-throughput lead discovery systems. Partial and full automation of biochemical and biotechnological workflows is therefore rapidly developing [1,2]. This does also involve surgical pathology laboratories [3,4]. The degree of laboratory automation

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depends on the integration of individual devices such as liquid handlers, analysers, samplers and other standalone instruments, into an automated workflow that operates without human intervention [1]. However, even though laboratory automation and its accompanying hardware and software technologies are constantly evolving, the implementation of these technologies still lacks effective plug-and-play functionality. Thus, highly time-consuming and expensive integration efforts from user perspective are necessary for the realization of laboratory automation approaches.

Reviews by Lippi and Rin [1], Hess et al. [5], Christensen et al. [2], Bai et al. [6], Hussnaetter et al. [7], Munari et al. [4] and Biermann et al. [8] address a wide range of topics related to laboratory automation. Lippi and Rin [1] primarily focus on the advantages and disadvantages of automation in the high-throughput life science industry. They consider various aspects such as profitability, psychological effects and risks among others. In the review of Hess et al. [5] an application specific use case in the life science field is investigated in detail. Covering the topic of next generation sequencing the authors examine several methods for automated library preparation. Christensen et al. [2] considers the key aspects towards process automation in the field of synthetic chemistry. Staying in the chemistry field, Bai et al. [6] focus on the overall software and data structure required for laboratory automation. A more application specific insight is given by Hussnaetter et al. [7] dealing with methods for the automation of enzymatic glycan synthesis. Munari et al. [4] provide a comprehensive overview of the current state of laboratory automation in pathology. In the review of Biermann et al. [8] in particular, the biotechnological field is examined in more detail. The authors give insights into major requirements needed for automation such as mechanical- and communication interfaces. A limited amount of detail is provided on the basic structure of automated processes. This includes the hardware components required to automate essential basic laboratory operations that are typically performed by humans. Additionally, in-depth information on current advances of a broad range of existing hardware and software technologies are not in the focus of the authors [8].

A general overview of non-application specific laboratory automation technologies including necessary software and hardware infrastructure is missing. Beside automation in specific areas such as life science and synthetic chemistry, this includes the accompanying preparative processes that are carried out in biotechnological laboratories. These flexible workflows cover buffer or eluent preparations, dilution series preparations and on-demand analytical measurements among others. Technical application areas of these

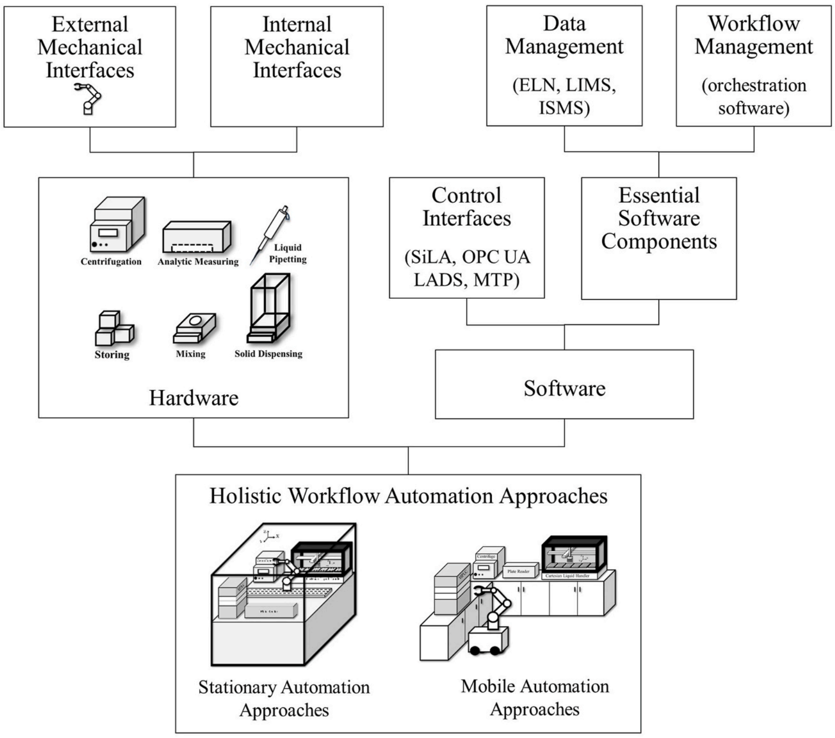

Fig. 1. Hierarchical overview of the field of laboratory automation and its individual components. To achieve holistic workflow automation (Section 2.4), regardless of whether it is mobile or stationary, hardware (Section 2.2) and software (Section 2.3) components are required. The hardware comprises automated solutions for individual basic laboratory operations such as liquid pipetting (Section 2.2.2), solid dispensing (Section 2.2.3), mixing (Section 2.2.4), storing (Section 2.2.5), centrifugation (Section 2.2.6) and analytic measuring (Section 2.2.7). The internal interfaces on the devices themselves as well as the external interfaces covered by robots (Section 2.2.1) are particularly essential. The software components are divided into essential software components (Section 2.3.1) and required control interfaces (Section 2.3.2). The essential software components comprise workflow management through orchestration software and data management through electronic notebooks (ELN), laboratory information management systems (LIMS) and inventory and sample management systems (ISMS). Control interfaces include, for example, Standardization in Laboratory Automation Standard (SiLA), Open Platform Communication Unified Architecture Laboratory and Analytical Device Standard (OPC UA LADS) and Module Type Package (MTP).

workflows range from research and development to quality control and production with comparable requirements along the process chain.

This work provides a structured overview of advances in non-application specific laboratory automation. The review gives an insight into the basic software and hardware infrastructure required for holistic workflow automation. From hardware perspective, we review the latest technologies for automating individual basic laboratory operations performed by humans independent of the final workflow. This includes developments in internal and external mechanical interfaces. From software perspective, progress in control interfaces as well as essential software components for data- and workflow management is investigated. Finally, holistic laboratory automation approaches are examined comprising mobile and stationary automation approaches (Fig. 1). In addition, advances with regards to plug-and-play functionality will be reviewed, and missing links will be identified.

2. Status quo of laboratory automation

2.1. Laboratory automation infrastructure

In laboratories the individual workflows consist of basic laboratory operations which are usually manually performed. They comprise operations such as liquid pipetting, solid dispensing, mixing, storing, centrifugation, analytic measuring as well as transferring and gripping. To complete workflows, humans coordinate the individual basic laboratory operations accordingly. Along with that, documentation is performed manually. In the case of laboratory automation, the basic laboratory operations are mapped by automatized hardware components, and the coordination and documentation are handled by corresponding software components. Thus, there are two opposing components for successful laboratory automation.

1. the hardware as the physical and mechanical component required for process automation and

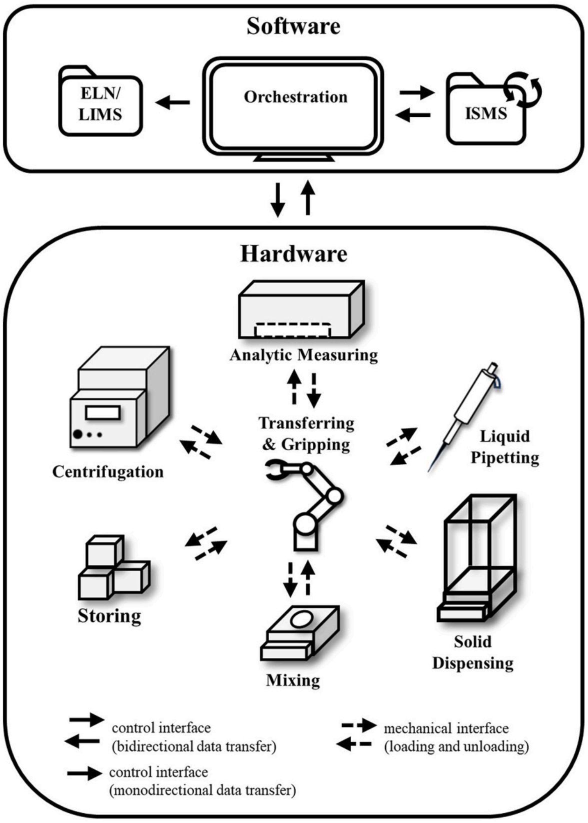

Fig. 2. Schematic representation of the overall software and hardware infrastructure required for laboratory automation. A robot for automated transferring and gripping (Section 2.2.1) is depicted in the centre. The robot operates and connects hardware representing further basic laboratory operations such as liquid pipetting (Section 2.2.2), solid dispensing (Section 2.2.3), mixing (Section 2.2.4), storing (Section 2.2.5), centrifugation (Section 2.2.6) and analytic measuring (Section 2.2.7). Mechanical interfaces between the individual hardware components and the robot are required for proper interaction such as for loading and unloading of the hardware components. Control interfaces between the hardware and an overarching software promote bidirectional communication. Bidirectional communication occurs also between the orchestration software and the inventory and sample management system (ISMS). Monodirectional communication occurs between the orchestration software and a corresponding electronic notebook (ELN) or laboratory information management systems (LIMS).

2. the software as the basic requirement for effective collaboration of the hardware components as well as data storage and digitalization.

They work in close cooperation with each other (Fig. 2).

The hardware components depict the various basic laboratory operations needed for the realization of a workflow. They are individually already highly automated in standalone devices [9,10]. This includes liquid pipetting-, solid dispensing-, mixing-, storing, centrifugation-, and analytic measurement devices.

The software component is the logical element required for workflow automation and is responsible for digitalized data storage and most importantly workflow coordination. It includes software like orchestration software, electronic notebooks (ELN), laboratory information management systems (LIMS) and inventory and sample management systems (ISMS) [2–4,11–13].

For cooperation between hardware and software components, appropriate interfaces are required that define the degree of plug-and-play functionality for laboratory automation [1,8,12,14]. There are two types of interfaces.

1. mechanical interfaces for physical connectivity between hardware devices and
2. control interfaces for digital connectivity between hardware and software.

Control interfaces are a crucial limiting factor for plug-and-play integration. Standalone hardware devices tend to use closed vendor specific interface protocols. Due to such proprietary interfaces, remote control is often not possible, so manual operation of hardware devices is required to start workflows directly on the devices [6,8,12]. Especially, for plug-and-play functionality, meaning simple and rapid software and hardware integration in an automated workflow, proper control interfaces are essential [12]. Software components, including process coordinating orchestration software, require suitable control interfaces to enable remote control and data transfer with the corresponding hardware elements involved in the process. Likewise, the control interface between this so-called orchestration software and other higher-level laboratory software such as ELN, LIMS or ISMS are essential for proper data exchange (Fig. 2) [2,8,11–13]. These software internal interfaces tend to be less problematic compared to hardware specific control interfaces since such software like ELNs, LIMSs and ISMSs are usually developed for the sake of digitalization and automation.

Mechanical interfaces on the other hand can be further divided into two categories.

1. external mechanical interfaces for physical connectivity and transferring of objects between instruments and
2. internal mechanical interfaces for physical operation of instruments comprising loading and unloading devices.

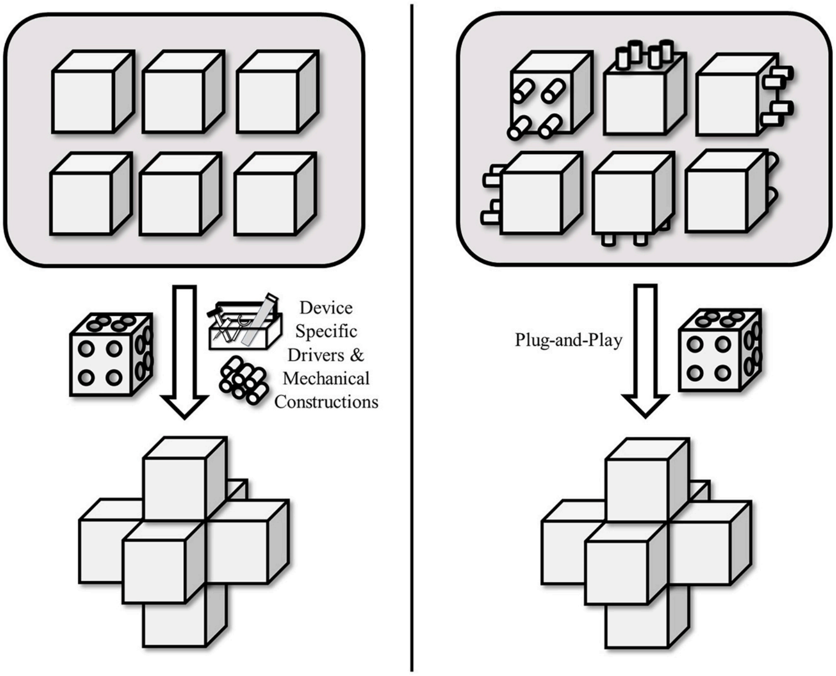

Fig. 3. Schematic representation of plug-and-play integration. On the left-hand side plane cubes without standardized control and internal mechanical interfaces are depicted. They need to be further extended by respective pins representing device specific drivers and mechanical constructions to fit into the holes of a central cube to form the final structure. On the right-hand side existing pins representing standardized control interfaces and sufficient internal mechanical interfaces on the cubes enable simple and fast plugging of the cubes with a central cube with corresponding holes for plug-and-play integration.

External mechanical interfaces include mobile robots, linear axes and robotic arms equipped with various grippers. They automate the basic laboratory operation of transferring and gripping of objects. This area of external mechanical interfaces is already well-developed and prepared for use in laboratory automation applications [2,12,15,16].

Internal mechanical interfaces involve the automated operation of specific hardware devices, as these are typically designed for manual handling. They have manual loading and unloading mechanisms for example. These interfaces are determined by the hardware itself and can only be modified to a limited degree, as they are vendor-specific [8,12,17].

Finally, two major factors highly influence the extent of plug-and-play functionality of hardware and software.

1. control interfaces and
2. internal mechanical interfaces.

A lack of such interfaces usually leads to costly and time-consuming integration efforts. Thus, complicated workarounds from user side are required to overcome insufficient interfaces (Fig. 3). For example, device specific drivers are used to overcome the lack of standard non-proprietary control interfaces [13,18]. For cases where internal mechanical interfaces are lacking, mechanical work-arounds, like specially designed grippers or additional hardware elements, are developed to handle manual doors, for instance Ref. [17].

2.2. Hardware approaches

A concise overview of the commonly available hardware technologies is provided. Furthermore, various approaches for external mechanical interfaces for connecting standalone devices are examined.

2.2.1. Robots for automated transferring and gripping

Starting with the most essential basic laboratory operations, the transferring and gripping of objects, automation is achieved through the use of various robotic systems. Robots often serve as external mechanical interfaces, connecting different hardware components needed for workflow automation. There are a couple of external mechanical interface approaches for achieving successful automated transportation of objects between hardware components as well as for gripping of objects such as well plates, tubes, bottles or racks with tissue samples [2–4,8,19].

External mechanical interfaces for transportation can be divided into four different categories [2,12].

1. Cartesian systems,
2. SCARA (selective compliance assembly robot arm) robots,
3. multiple-axis- and dual-arm robotic systems and
4. autonomous mobile robots.

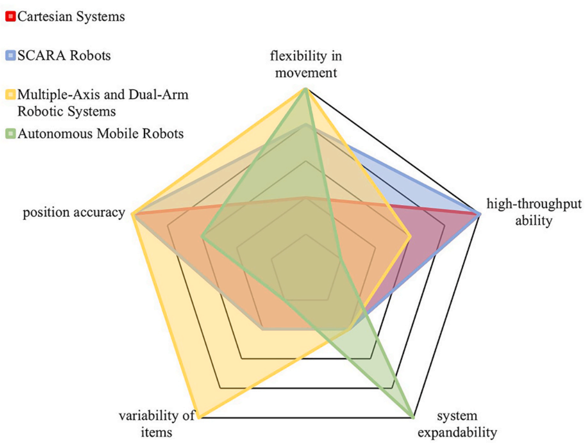

Fig. 4. Comparison of Cartesian systems, SCARA robots, multiple-axis- and dual-arm robotic systems, and autonomous mobile robots (AMRs) according to flexibility in movement, high-throughput ability, system expandability, variability of items and accuracy. The outermost radius corresponds to the highest value of a property while the innermost radius corresponds to the lowest value. Cartesian systems and SCARA robots show increased high-throughput ability. However, system expandability and variability of items is limited. Considering flexibility, SCARA robots have a higher flexibility in movement compared to Cartesian systems. The highest flexibility in movement is achieved by AMRs and multiple-axis- and dual-arm robots. Even though they have a lower high-throughput ability and system expandability, multiple-axis- and dual-arm robots score with a high variability of items they can handle. In contrast AMRs show a high system expandability with a low variability of items they can handle. Apart from AMRs all systems have a very high position accuracy.

Depending on the overall automation approach, different mechanical interfaces can be considered. To determine the appropriate external interface for automating a specific process, the following criteria must be evaluated (Fig. 4).

1. flexibility in movement meaning the ability to reach various positions in a three-dimensional room,
2. high-throughput ability,
3. system expandability so that the system of devices operated by the robot can be expanded as required,
4. variability of items meaning the handling of various container types and
5. position accuracy when transporting, picking and placing objects.

Cartesian systems are widely used for automation in the life science field. They are based on xyz-linear axes reducing their flexibility in movement to three degrees of freedom. End effectors are attached to the end of the z-axis. They differ depending on the intended use of each individual system. For instance, considering Cartesian liquid handlers the end effector comprises a pipetting module. Also other types of end effectors like two-point-grippers, plate grippers and needles to name some of them can be attached to the z-axis [2,3,10,20–22]. Cartesian systems tend to be encased because of safety issues. Thus, they represent fully isolated systems with reduced system expandability options. They are usually also limited to specific container types like well plate formats and are thus limited in the variability of items they can handle. This forces users to adjust their desired workflow that is to be automated to the format of the system. However, the systems have increased high-throughput ability and high position accuracy [21–24].

SCARA [25] robotic arms follow a different approach. These robotic manipulators with four degrees of freedom are comparable to Cartesian systems, as they move along the xyz axes. Due to their fourth degree of freedom, the rotary movement, they have a higher flexibility in movement than Cartesian systems and are better suited when it comes to loading or unloading of devices with a blocked head area such as encased balances or microscopes [2,16]. Accordingly, they can operate a higher variability of devices. As Cartesian systems SCARA robots primarily handle well plate formats resulting in a low variability of items they can handle. Due to their fixed positions, these systems have a limited range of motion, restricting possibilities for system expandability with additional devices. With their high speed and position accuracy, SCARA robots have extensive high-throughput ability [2,25–28].

Multiple-axis- and dual-arm robotic systems are among the most flexible robotic solutions available. In contrast to the previously mentioned systems, these robots have more than four degrees of freedom. This includes robotic arms with six to seven degrees of freedom or dual-arm robots with even more than seven degrees of freedom [2,29–31]. These multiple-axis robotic systems excel in automating lower throughput laboratory workflows that require a high degree of flexibility in movement and position accuracy. They can handle a high variability of items and devices using corresponding end effectors [17,29]. As for SCARA robots, multiple-axis- and dual-arm robotic systems are fixed positioned resulting in a defined range of motion limiting the system expandability.

Autonomous mobile robots (AMRs) can drive independently in a laboratory. In contrast to autonomous guided vehicles (AGVs), AMRs do not need any predefined paths or navigation support. They use their own sensors to detect their surrounding and react in an *ad-hoc* manner. Due to this independent navigation ability and their high flexibility in movement, AMRs are suited for usage in laboratories. Such robots are particularly advantageous when the coexistence of humans and robots in the same laboratory environment is desired, as they can autonomously navigate through the existing laboratory. This also results in simple system expandability when additional devices need to be integrated into an automated workflow and further access points need to be reached [12,32–36]. Particularly in the case of automation of non-high-throughput workflows these approaches may be beneficial compared to larger encased Cartesian systems. Due to their reduced position accuracy and variability of items they can handle, AMRs are usually combined with robotic manipulators such as SCARA-, multiple-axis- or dual-arm robots. This results in a so-called *Mobile Manipulator* [2,12,15,16,35,37].

Among the four categories, Cartesian systems and SCARA robots are the preferred methods for the life science field, particularly in high-throughput lead discovery, sequencing, and assay research. For on-demand preparative workflows, such as buffer preparations or analytical measurements that require high flexibility in movement and a high variability of items to be handled, multiple-axis- and dual-arm robotic systems can be used. If subsequent system expandability is desired, AMRs are well-suited.

In combination with the diverse automated transportation technologies, the corresponding end effectors for gripping the objects to be transported are essential. They are mounted at the last axis of the respective robotic arm. According to their operating principal, grippers can be categorized in pneumatic and electric grippers. This categorization depends on the media available in the system, the objects being handled and the application field. Pneumatic grippers operate through compressed air and electric grippers through electricity. The shape of the grippers is influenced by characteristics such as size, geometry, surface material and physical properties of the objects being handled. Independent of the operating principal different force types comprising mechanical force, vacuum force or magnetic force can be used. Multiple finger grippers make use of mechanical force for gripping of objects. Vacuum and magnetic grippers typically use a specifically formed contact surface in combination with vacuum or magnetic force for gripping of objects [8,19,38].

2.2.2. Automated liquid pipetting

Liquid pipetting is a crucial basic operation performed in every laboratory dispensing small liquid volumes in the range of 1 µL to 5000 µL. There are several significant factors that have to be considered for proper pipetting performance according to International Organization for Standardization (ISO) 8655 [39,40]. Accurate manual pipetting is not only influenced by appropriate equipment but also pipetting technique as well as environmental factors among others [39–41].

Manual liquid pipetting is often very time-consuming and can cause additional health consequences for humans, especially if this activity is performed repetitively in constantly high quantities [42]. Furthermore, human error is a significant factor when it comes to variances in pipetting precision [43–45]. To overcome this risk of manual pipetting related injuries and lack of precision, two major automated liquid handling approaches (Fig. 5) are established at the moment [20,44,46–51].

1. Cartesian liquid handlers and
2. multiple-axis- and dual-arm robots handling manual pipettes.

The two approaches differ in five major characteristics comprising.

1. flexibility in pipetting angle to be able to pipette into various container types and laboratory devices,
2. high-throughput ability,
3. commercial availability,
4. variability of items meaning the handling of various container types and
5. pipetting accuracy, ensuring precise liquid pipetting by the system.

Accordingly, a comparison of the two approaches is conducted with respect to these characteristics (Fig. 6). Evaluating the two methods based on these criteria allows users to determine which method is best suited for their application.

Cartesian liquid handlers are limited to a Cartesian, linear axis robotic workstation with three degrees of freedom (xyz-axis) [5,20,46,48,52]. The linear axis contains the pipetting module in the z-direction and pipettes at a 90° angle into specified container types. This results in a reduced flexibility in pipetting angle. Since the linear axis with the pipetting module is permanently connected to the workstation, these devices are often designed solely for use with system-specific, predefined container types. In addition, the container types are often limited to well plate format leading to a low variability of items they can handle. The reduced flexibility in pipetting angle and variability of items leads to a high-throughput ability of the systems [23,24,46,48]. Cartesian liquid handlers are already well established in today's laboratories and commercially available. Due to integrated sensors such as for liquid level detection the devices have a high pipetting accuracy [50].

Cartesian liquid handlers have a high commercial availability. For instance, *Hamilton Company* and *Tecan Group Ltd.* offer a variety of solutions in this field. Beside benchtop single- and multi-channel liquid handling systems, both companies offer highly automated modular platforms that are not only limited to liquid handling but can also perform gripping and transferring tasks using robotic arms. Such robotic arms are usually incorporated into a linear axis and capable of moving in three degrees of freedom. These highly automated modular platforms can incorporate additional lab devices like plate readers, heating and cooling modules, mixing devices, storage modules and barcode readers to name some of them [5,53,54]. Nevertheless, this modularity is still mostly limited to standardized well plate and standardized sample tube handling. Additionally, both companies tend to be limited to the use of their own proprietary software and programming language. Current liquid handling platforms on the market are for example the *Tecan Fluent*® and the *Tecan Freedom EVO*® as well as the *Hamilton Microlab Prep, Microlab STAR* and *Microlab VANTAGE*. The systems deliver high quality results with low error rates [10,50,53,54].

Multiple-axis- and dual-arm robots handling manual pipettes are considered as the counterpart to Cartesian liquid handlers (Fig. 5). The approach does not focus on high-throughput ability but on flexibility in pipetting angle and on variability of items the systems can pipette into. The robotic arms handle single- or multi-channel manual or electronic pipettes [20,47,55–58]. They can mimic human movements and perform pipetting in flexible manner. This applies especially to a minimum of six degrees of freedom. With more degrees of freedom compared to Cartesian liquid handlers, these systems enable a high flexibility in pipetting angle allowing them to perform pipetting tasks at various angles. In contrast to Cartesian liquid handlers, multiple-axis robotic arms are not necessarily combined with fixed workstations with predefined geometries. Instead, they can be mounted on an existing laboratory bench and handle containers placed on the bench. This leads to the high variability of items they can handle such as regular beakers, bottles, well plates or tubes [29,47]. However, such multiple-axis robotic arm approaches handling manual pipettes suffer from lacking internal

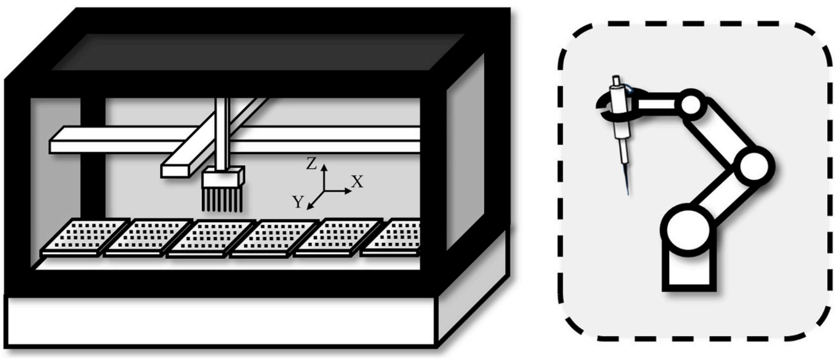

Fig. 5. Schematic representation of a Cartesian liquid handler on the left-hand side and a multiple-axis robot handling a manual pipette on the right-hand side. The Cartesian liquid handler comprises a linear axes system with three degrees of freedom (xyz). A multi-channel pipette end effector is mounted at the z-axis and pipettes into well plates.

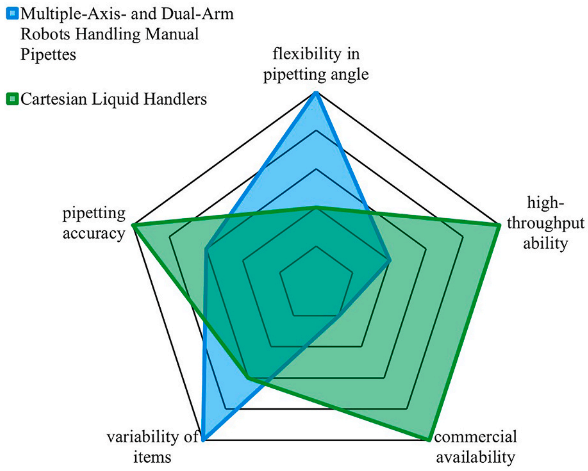

Fig. 6. Comparison of Cartesian liquid handlers with multiple-axis- and dual-arm robots handling manual pipettes according to flexibility in pipetting angle, high-throughput ability, variability of items, commercial availability and pipetting accuracy. The outermost radius corresponds to the highest value of a property while the innermost radius corresponds to the lowest value. Cartesian liquid handlers show a very high pipetting accuracy compared to robots handling manual pipettes. Additionally, their commercial availability and high-throughput ability is higher. In contrast multiple-axis- and dual-arm robots handling manual pipettes show a higher flexibility in pipetting angle and variabilities of items they can handle.

mechanical interfaces from the pipette perspective. Since manual pipettes are designed for human use, feedback response on the success of the pipetting process relies on human vision. Lacking sensors of the pipette for proper feedback response can influence pipetting performance and lower pipetting accuracy compared to Cartesian liquid handlers. In addition, such approaches have low commercial availability but have to be integrated subsequently by the user or a system integrator.

Dual-arm robotic systems in particular are preferably used as automatic liquid handlers, as they can perform human-like movements with their multiple degrees of freedom [20,55–59]. These robots consist of two robotic arms, in this case each with seven axes of manipulation and a single axis of rotation. For the use of manual pipettes one arm holds a regular manual pipette and the other arm presses the button for liquid dispensing [55–58]. Using manual pipettes presents several limitations, including challenges in volume adjustment due to their mechanical operation. As a result, other approaches often employ dual-arm robotic systems with electronic pipettes. These electronic pipettes can be integrated wirelessly via Wi-Fi or Bluetooth or with cable connection for example using a *RS232* communication protocol. The choice of integration depends on the respective use case. Using such electronic pipettes allows variable automated volume adjustment of the pipette through the respective pipette software. In addition, the pipetting process does not require the use of both robot arms [20,59]. An alternative to the use of dual-arm robots is the use of six- or seven-axis robotic arms. In this case the end effector design of the robotic arm is able to hold the pipette and simultaneously press the button for liquid

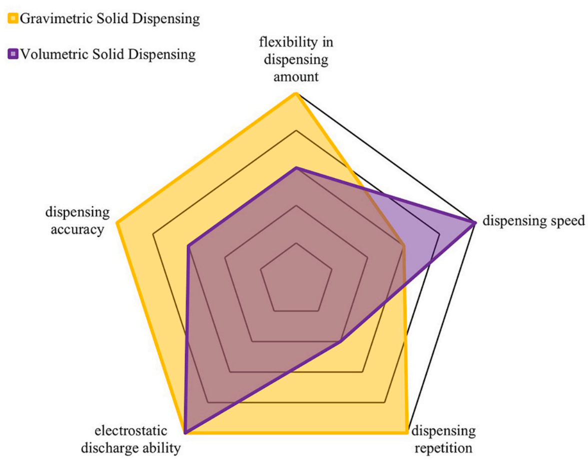

Fig. 7. Comparison of gravimetric solid dispensing with volumetric solid dispensing according to flexibility in dispensing amount, dispensing speed, dispensing repetition, electrostatic discharge ability and dispensing accuracy. The outermost radius corresponds to the highest value of a property while the innermost radius corresponds to the lowest value. Gravimetric solid dispensing shows higher dispensing accuracy, flexibility in dispensing amount and dispensing repetition compared to the volumetric method. Regarding electrostatic discharge ability both methods make use of antistatic methods. Considering dispensing speed, the volumetric method is the faster method.

dispensing [29,51].

Finally, Cartesian liquid handlers are predominantly used in the life science field for high-throughput lead discovery, sequencing and assay research [5,46,48,52]. In contrast, multiple-axis- and dual-arm robots handling manual pipettes are better suited for use in preparative and flexible on-demand applications. This includes often altering workflows such as buffer preparations and analytical measurements [20,55–57].

2.2.3. Automated solid dispensing

Solid dispensing is a significant basic laboratory operation. Manual execution can be highly time-consuming and exhausting, especially when dealing with small solid dosing amounts in the milligram range. Additionally, accuracy may suffer when dosing very small amounts of solids in the milligram range. Especially with regard to electrostatic charging of solids, manual execution can be not only very time-consuming but also inaccurate. Considering that solid chemicals tend to bear several health risks, automation of this task would lead to advantages such as health-safety, higher accuracy and higher efficiency among others [2,60–62].

One major challenge when it comes to automated solid dispensing is the morphology of solids. They range from powdery and free-flowing solids to sticky and hygroscopic solids influencing their ability of being dispensed by current state-of-the-art automated solid dispensing technologies [2]. The current technologies are based on two different methods [50,63,64].

1. volumetric solid dispensing and
2. gravimetric solid dispensing.

The two methods are compared according to five characteristics influencing the dispensing process (Fig. 7). They include.

1. flexibility in dispensing amount comprising the quantity of dispensable solid,
2. dispensing speed defining the required time frame until the desired solid quantity is dosed,
3. dispensing repetition meaning the ability to constantly reach the predefined quantity of a dispensed solid,
4. electrostatic discharge ability and
5. dispensing accuracy so that the actual dispensed quantity equals the supposed quantity.

Depending on the users' needs and the overall workflow being automated, different characteristics become important.

Volumetric solid dispensing tends to be very fast compared to gravimetric dispensing since it is based on dispensing predefined portions. They are defined by corresponding dosing heads. A target volume is reached by dispensing multiples of a preset volume achieving high dispensing speed. The method lacks flexibility in dispensing amount if the desired quantity to be dosed cannot be accurately mapped by multiples of the predefined volume of the dosing head. In addition, since dispensed solid amounts are not controlled through weighing after dosing, the method lacks dispensing accuracy. This is especially the case when considering a change in the solid behaviour due to physical properties of solids. For instance, a change in the particle size of a solid due to hygroscopic properties can influence its volume and lead to inaccurate portions [50,64]. This also leads to a lower dispensing repetition compared to gravimetric approaches. In regard to electrostatic discharge ability both technologies make use of antistatic methods such as ionizers or antistatic materials to avoid or decrease electrostatic charging of solids [63,65–67].

An example of automated solid dispensers utilizing the volumetric method are the systems provided by *XQ Instruments* [67]. The systems dispense solid in the milligram to gram range. Besides, *Zinsser Analytic* [68] offers solutions such as the *Zinsser REDI Tool* capable of dispensing solids in the sub milligram to low milligram range [50,68].

Gravimetric solid dispensing is based on continuous measuring of the solids weight until the target amount is reached. This results in a higher flexibility in dispensing amount that can be dosed. Additionally, a higher dispensing accuracy and repetition is granted compared to the volumetric method. However, regarding speed the gravimetric approach is slower than the volumetric approach, since it does not dispense predefined portions [50,64].

For gravimetric solid dispensing the *Mettler Toledo XPR Automated Balance* [66] and the *Chemspeed Crystal Powderdose* and *the Crystal Swile* [65] are discussed in further detail since they are widely used in academia and industry. The *Mettler Toledo XPR* system is based on a funnel-principle using a rotating tapping movement caused by vibration leading the solid flow to the exit of the funnel shaped dosing head. It is therefore suitable for dosing solids in the milligram range [2,50,60,61,69]. Also, the *Chemspeed Crystal Powderdose* is based on a funnel-principle and a worm thread. The solid is dispensed by quickly opening and closing the bottom of the dispensing container. It is also suitable for dosing solids in the milligram range [60,69,70]. The *Chemspeed Crystal Swile* is based on a displacement-principle, in which a capillary is moved up and down with the help of a piston and thereby absorbs the solid. This makes it particularly suitable for dosing in the sub milligram to low milligram range [2,50,60,69]. In summary, the *Mettler Toledo XPR* and the *Chemspeed Crystal Powderdose* are potentially more effective for dispensing powdery solids, whereas the *Chemspeed Crystal Swile* is suitable for dosing sticky and clumpy solids as well as oils [2]. One tremendous difference between the technologies of *Mettler Toledo* and C*hemspeed* is the weighing method they use. The *Mettler Toledo XPR* uses a regular precision balance where the solids are dispensed on, so the solid is weighed after being dispensed when it appears on the scale. The *Chemspeed Crystal* is based on an integrated weighing module inside the dosing module that ensure indirect weighing of the solid while dispensing [60,69].

These two solid dispensing systems from *Mettler Toledo* and *Chemspeed Technologies AG* are well established for small scale automated solid dosing [2,61,69–71]. Nevertheless, both technologies are limited to the physical properties of the solids they can dispense. In addition, they require the desired solid to be transferred prior to usage to the respective dosing heads that bear the risk of blockage by bigger solid particles. Returning to dual-arm robotic systems, another automated approach for small-scale solid dispensing focuses on mimicking human behaviour by using a spatula and a scale. With this approach solids between milligram and gram range can be dispensed. The approach aims to overcome the risk of dosing head blockage by bigger particles, as reported by Jiang et al. [60]. In their approach, the dual arm robot uses different sizes of spatula for dispensing different solid amounts into vials on a precision scale. The scale has an incorporated funnel in the top of the housing to have a glass funnel placed inside pointing to the middle of the scale. Solid compounds are provided in a special open container. It is placed on top of the scale housing directly next to the funnel to reduce pathlength when transporting the solid with the spatula. The robot can open and close the door of the scale and place a vial inside of the scale under the glass funnel. However, open handling of solids can be disadvantages especially when it comes to handling hygroscopic solids [60].

After comparing both methods, volumetric solid dispensing can be used if rapid dispensing of non-hygroscopic, powdery solids is desired. In contrast, the gravimetric method is suited for dispensing of flexible amounts with high accuracy due to continuous weighing until the target amount is reached.

2.2.4. Automated mixing

Automated mixing or stirring of samples can be classified in two techniques.

1. contactless mixing which is primary focussing on automatic shaking techniques using vibration or inverting methods and
2. classic stirring using stirring compartments.

Shaking techniques are usually more preferred compared to stirring due to the risk of contamination by external stirring compartments [2,50]. Regarding shaking techniques, several systems for shaking different container types are available on the market. For example, classic vortex mixers tend to be used in many laboratories making use of vibration for homogenizing liquids. They can be used for various container types with different geometries like tubes and vials typically with volumes of up to 50 mL. In manual laboratories such devices are operated by humans holding the containers at the top pressing them against the shaking platform. For automation approaches this movement can be mimicked by robotic systems. Furthermore, there are also approaches of vortex devices with a fixation compartment to set the containers on the shaking platform. Well plate shaking is not realizable with these devices [50]. A different type of shaking device is the *Eppendorf ThermoMixer® C* which can handle tubes with up to 50 mL and well plate formats. Beside mixing the *Eppendorf ThermoMixer® C* is also able to cool and heat samples [72]. In addition, the company *IKA-Werke GmbH & Co. KG* offer diverse shaking devices with multiple attachments for different types of containers comprising flasks, bottles, tubes or well plates among others. Especially the *KS*- and *HS-control* series is ideally suited for automated integration of the devices since they offer internal mechanical-as well as control interfaces for automated usage [50,73].

In contrast to these contactless shaking devices there are also stirring devices that can be used for automated mixing. The *2mag AG* offers different types of magnetic stirrers for stirring multiple numbers of flasks or well plate formats. For automation use, they offer multiple control interfaces for their devices [50,74]. Besides, systems like magnetic stirrer with integrated scales as from *Gravitech GmbH* can be incorporated into automated workflows. They combine two major basic laboratory operations comprising weighing and mixing. This combination facilitates the preparation of liquid mixtures such as buffers since the desired liquid amount is weight resulting in higher accuracy compared to typical manual volumetric concentration adjustment. With an integrated *RS232* interface these magnetic stirrer-scales can be integrated in an automated workflow [75].

2.2.5. Automated storing

Automated storage systems can be divided according to the type of storage element they are storing. Particularly in terms of sample tube storage and well plate storage automated storage systems are far developed. Especially, for liquid handlers, supply companies like *Hamilton Company* [53] and *Tecan Group Ltd.* [54] provide systems that can be configured with their liquid handlers. Storage systems as used in the *Mettler Toledo Chronect XPR* are already available for other container types, such as solid dosing heads [66]. There are different sample storage systems according to the respective temperatures samples must be stored at. This does not only include storage at room temperature but also at $+4\,^{\circ}$C, $-20\,^{\circ}$C and $-80\,^{\circ}$C [76]. Besides, storing does include inventory of samples and containers for example by using barcode-, QR-code- or radio frequency identification- (RFID) technologies [3,4,50]. However, the market still lacks more flexible and versatile automated storage technologies for classic laboratory equipment beside sample tubes. Other types of laboratory equipment include bottles, flask, funnels, magnetic stirring bars in addition to regular small-scale tubes in the range of 1 to 50 mL. Systems in which regular laboratory consumables can be stored in a small scale for automatic use in an individual or mixed manner are not yet developed.

2.2.6. Automated centrifugation

Centrifugation as basic laboratory operation is required for solid-liquid-separation of samples or also for separation of liquids with different densities. There are several types of centrifuges. The devices differentiate, according to their application, in loading capacity, size, technique or acceleration. Depending on their size, they can handle different container types and accordingly have attachments to handle multiple container types within one centrifuge. Consequently, these devices are separated in benchtop centrifuges for smaller containers of up to 50 mL volumes and well plates and floor-standing centrifuges used for larger use cases for volumes of 100 to 1000 mL [50,77,78]. Centrifuges are already highly automated devices. The samples are placed in the centrifuge and, after selecting the desired program usually directly on the display of the device, they can be started for a certain time and work independently. When it comes to explicitly automated centrifuges, they are usually designated as robotic centrifuges that can be operated by a robot arm or a linear-axis system. They have a corresponding control interface, so that remote control is possible and various programs can be started without the need for human interaction. The companies *Hettich* and *Sigma* offer robotic centrifuges with respective internal mechanical interfaces for loading and unloading of the devices by robotic systems. Additional control interfaces enable communication with the devices for remote control and integration into an automated workflow [50,79,80].

2.2.7. Automated analytic measuring

The performance of analytical measurements, regardless of high-throughput or non-high-throughput preparative chemistry, is an essential basic laboratory operation. These devices are inherently highly automated due to the nature of their design and purpose. This includes photometers, mass spectrometers or analytical high-performance liquid chromatography (HPLC) devices. Further automation in this field occurs when it comes to autosamplers automatically providing a defined number of samples to be measured to the respective device [2]. However, internal mechanical interfaces or control interfaces for these devices are often difficult to handle. The lack of internal mechanical interfaces makes loading and unloading the devices difficult for robotic handling. Furthermore, proprietary software and control interfaces complicate integration. This usually results in complicated workarounds for integration into automation workflows [17]. In contrast, the market for life-science-high-throughput plate reader devices is already well established. There are several absorption- and fluorescence-based plate reader devices from different companies suitable for the integration in automated landscapes [50,81].

2.3. Software approaches

2.3.1. Essential software components

Orchestration software solutions are used for receipt processing during an automated workflow. They perform hardware control, workflow coordination and temporal sequence coordination [12,14,82,83]. Inventory and localization of consumables and samples during the automation workflow is performed using an ISMS. The systems are based on barcode, QR-code or RFID technology for tracking [13]. Digitalized data storage of analytical result and workflow information is ensured through software approaches such as LIMS and ELN [11,84–86]. Finally, for successful integration of laboratory automation workflows, appropriate control interfaces for successful communication between hardware and orchestration software as well as between the orchestration software and the LIMS, ELN and ISMS software are important (Fig. 8) [2,6,12–14].

An exemplary automated workflow infrastructure consists of an orchestration software storing the workflow recipes. The software sends commands required for workflow completion to the respective hardware components and in return receives their status for coordination of the next commands. Simultaneously, the orchestration software communicates sample and consumable information to the ISMS receiving real-time localization information back. Finally, the orchestration software communicates the performed workflow information and the analytical results to the ELN and LIMS (Fig. 8).

Numerous types of orchestrations software for automated workflow control already exist on the market. For instance, *Green Button Go* from *Biosero* [87], *Laboperator* from *Labforward* [88], *Cellario* from *HighRes Biosolutions* [89] and *Zenon* from *Copadata* [90].

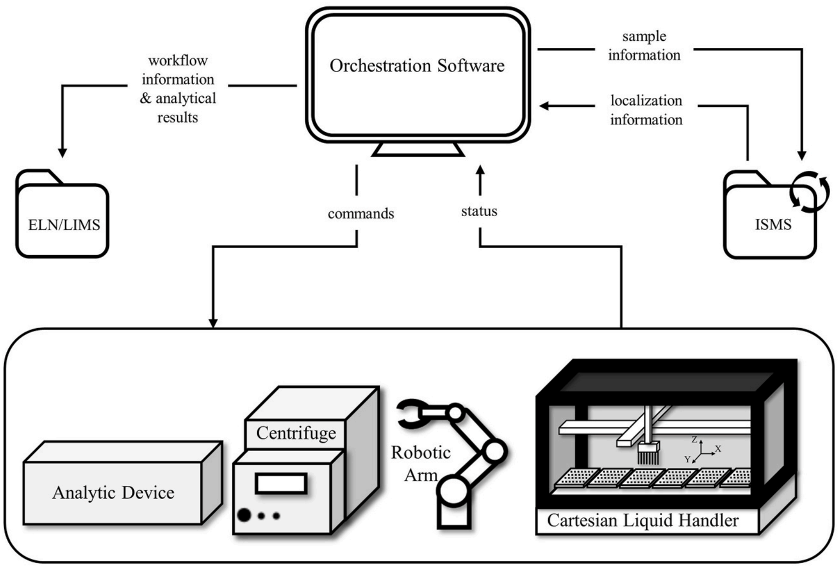

Fig. 8. Signal architecture between hardware and software. In this exemplary schematic overview four hardware components including an analytic device, a centrifuge, a robotic arm and a Cartesian liquid handler are coordinated to depict one workflow. The orchestration software sends commands according to the workflow requirements to the hardware components. In return the devices communicate their operating status back. The orchestration software communicates the information about samples and consumables to the ISMS and permanently receives the current localization of the sample or consumable. Finally, the performed workflow information and the analytical results are sent to the LIMS and the ELN.

2.3.2. Control interfaces

Vendors tend to use proprietary interfaces for their soft- and hardware, which creates difficulties when integrating these elements into a complete automation platform. Sometimes these proprietary interfaces make it even impossible to integrate the respective software or hardware into an automated workflow [6,8,12]. To simplify device integration, standardized communication protocols are required. Currently, there are three major communication standards that offer great potential for use in laboratory automation workflows [91].

1. *Standardization in Laboratory Automation* Standard (SiLA),
2. *Open Platform Communications Unified Architecture Laboratory and Analytical Device* Standard (OPC UA LADS) and
3. *Module Type Package* (MTP).

Especially the SiLA [92] and the OPC UA LADS standard [93] are commonly discussed in diverse laboratory automation publications [6,8,12–14,94]. *Module Type Package* (MTP) [95] is mainly used in process plant automation [96,97].

SiLA is a feature-oriented communication standard defining specific attributes and parameters to a feature of a device. A feature includes the various functions of a laboratory device. In the SiLA standard those devices represent servers. Each server has corresponding features that can be retrieved by a client, for example an orchestration software [12–14]. SiLA is based on the *Analytical Information Markup Language* (AnIML) which is widely used for data handling working with analytical measurement devices [13,92,94,98,99].

LADS, an application-oriented standard, is a companion specification of the industrial OPC UA standard. According to Brendel et al. [93], LADS is described a broader standard compared to SiLA. Their statement is based on the ability of LADS to control not only laboratory devices but also industrial devices and to exchange data with sensors for example. Additionally, the authors mark the LADS standard as a highly secure standard since it is linked to the security of OPC UA [93]. Wolf et al. [12] declare SiLA to be better suited for the use in life science research and development laboratories whereas LADS may be better suited for quality control and production environments due to its relation to the OPC UA industry standard.

MTP is a further OPC UA based standard. Even though MTP is rather used in process plant automation it is considered as qualified for laboratory automation. Other than SiLA and LADS, MTP does not focus on individual devices but on a group of devices operating together, so-called process equipment assemblies (PEAs). Thus, in process plant automation one MTP file representing all functions of a PEA is loaded into the overall process orchestration layer (POL) leading to a high modularity and flexibility in the process automation workflow [96,97]. This high degree of modularity and flexibility enables simple and fast device integration in the sense of plug-and-play laboratory automation.

Currently none of the three approaches is available for standard laboratory devices in a sufficient manner. This means that there are only a few laboratory devices, primarily in the life science sector, that include standardized communication protocols in their basic equipment configuration. In addition, this is usually limited to the SiLA standard [50]. Various bridging solutions are used for the plurality of common devices. Thus, workaround approaches are often used by users and companies like *Biosero*, *Labforward*, *HighRes Biosolutions* and many other system integrators and laboratory automation companies. This workaround solution comprises the development of individual device specific drivers for communication with the device based on their respective interface protocol [13,18,50,87–89].

2.4. Holistic workflow automation approaches

Comprehensive automation approaches that leverage individual standalone technologies to achieve holistic workflow automation can be divided into two main categories.

1. stationary automation approaches and
2. mobile automation approaches.

The two approaches differ in the following criteria.

1. flexibility in process variation meaning the ability to change the automated workflow running on the system,
2. high-throughput ability,
3. human-robot coexistence so that devices can additionally be operated by humans,
4. system expandability to include further laboratory devices into the workflow and
5. process reliability to ensure that the process can run consistently.

Depending on the user application and the number of workflows to be automated, different criteria are important (Fig. 11).

Stationary automation approaches are typically limited to a defined workspace and are usually enclosed due to safety requirements. They consist of fixed-position hardware devices arranged around robotic manipulators and/or conveyor belts for physical connection of the devices. Such robotic manipulators include SCARA robots, multiple-axis robotic systems and dual-arm robots for example. To increase reach and flexibility the robots are often combined with linear axes. In this case the arm is moving along a fixed x- and/or y-axis extending their overall degrees of freedom [1,18,29,55,100]. The robotic arm is typically mounted on top of the moving linear axial system and operates laboratory equipment such as centrifuges, plate readers, Cartesian liquid handlers and HPLCs arranged around it (Fig. 9).

Two examples for stationary holistic laboratory automation approaches will be examined in greater detail [18,55]. The *StemCellDiscovery* from Ochs et al. [18] is a stationary solution for high-throughput use in life science discovery research specifically used for cell cultivation. The system follows a Cartesian enclosed environment with a six-axis robotic arm fixed on a linear axis. The robotic manipulator is encircled by various standalone life science laboratory devices. As external mechanical interface the robot physically connects and operates these devices. The devices include an incubator, a centrifuge, a plate reader, a decapper, a microscope and a Cartesian liquid handler. The whole system is primarily handling well plate formats and tubes. The software approach uses a standardized communication middle layer, so-called *software agents*, translating commands between the individual executing laboratory device and the overarching control software for workflow orchestration. Arising from the challenge of proprietary and individual device interfaces this workaround acts as a standardized interface communication protocol layer. These so-called software agents however comprise device specific drivers for standardized communication to the upper orchestration software. With this, the authors intend to use a modular and extendable software approach for simple integration of new devices into the platform [18]. Similar approaches are described by Daniels et al. [101] with the development of a high-throughput screening platform and Waldenmaier et al. [102] who developed a high-throughput mass spectrometry analysis platform. These two approaches use *Cellario* from *HighRes Biosolutions* also integrating laboratory devices through device specific drivers [89,101,102].

In contrast to these life science approaches, Fleischer et al. [55] developed a stationary solution intending to automate more flexible processes, for example, those carried out during analytical measurement sequences. Similar to the approach of Ochs et al. [18] the system includes a robotic manipulator in a segregated environment. This robotic manipulator comprises a dual-arm robot capable of performing human like movements and operation of manual laboratory equipment using various gripper end effectors. The dual-arm robot is positioned in the centre of a laboratory bench with fixed positioned manual laboratory equipment and handles various types of consumables. For example, instead of operating an automated liquid handler the robot performs liquid handling using regular manual pipettes. Furthermore, the robot is capable of capping and decapping vials without the need of an external decapping device. These are two examples representing the aim of the authors to perform position independent manual tasks in the surrounding of the robot. Other commonly manually used equipment operated by the robot comprise the autosampler of a HPLC, an ultrasonic bath or a thermoshaker, among other [55].

Mobile automation approaches are considered an alternative to stationary systems. In this case a robotic manipulator is mounted on top of an AMR rather than a linear axis. In this case the approach takes advantage of the multiple degrees of freedom of the robotic manipulator and the autonomous mobility of the AMR in the room. A significant distinction from stationary systems is that the mobile robotic system can be integrated directly into existing laboratory environments. Consequently, there is no requirement for constructing a dedicated segregated working area around the robot, owing to the enhanced flexibility in movement afforded by the AMR. It can be introduced in a classic laboratory environment operating several laboratory devices placed on the benches [15,16,37]. Such devices for example include centrifuges, Cartesian liquid handlers, plate readers or other analytical devices like HPLCs (Fig. 10).

Considering mobile automation approaches two examples will be discussed in detail. The initial approach concentrates on high-throughput applications in the life sciences field, specifically involving the handling of well plates [16]. The second approach deals with a more flexible process in which more diverse container types are handled [15]. In the life-science-high-throughput field the *Frauenhofer IPA research Institute* published *Kevin* [16] a mobile manipulator for performing transportation tasks in life science

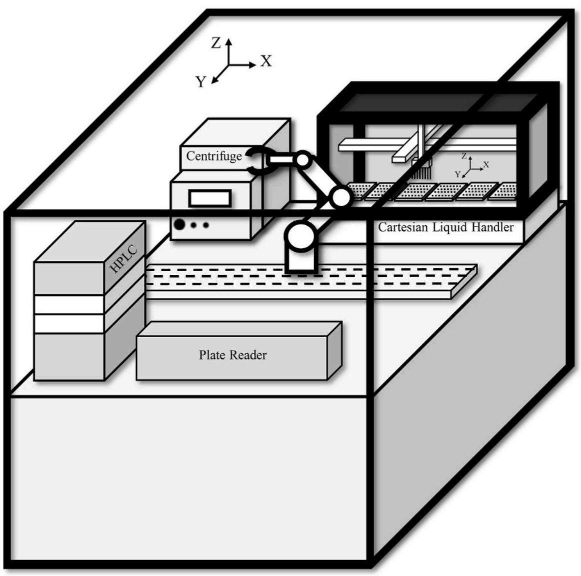

Fig. 9. Schematic representation of a stationary automation system. A robotic manipulator is mounted on a moving linear axis operating a Cartesian liquid handler, a centrifuge, a high-performance liquid chromatography (HPLC) and a plate reader.

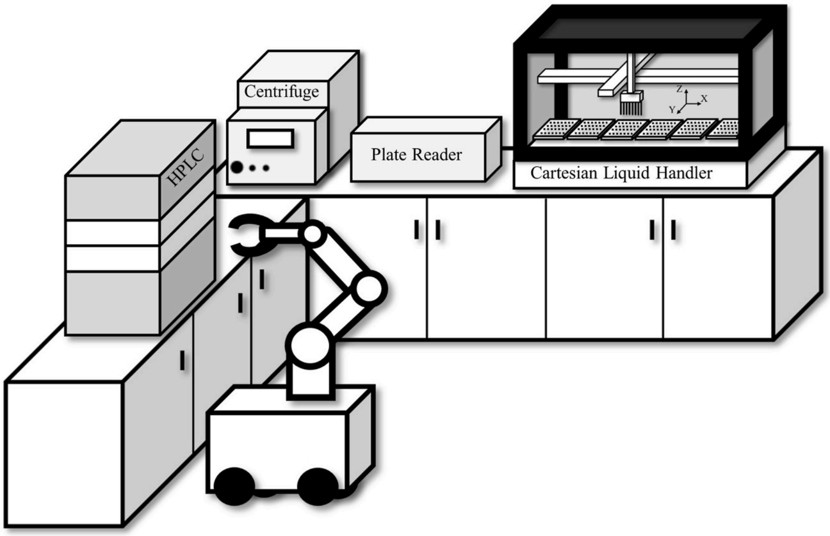

Fig. 10. Schematic representation of a mobile automation system. A robotic manipulator is mounted on an autonomous mobile robot (AMR) driving around in a laboratory. The mobile manipulator operates a Cartesian liquid handler, a centrifuge, a high-performance liquid chromatography (HPLC) and a plate reader.

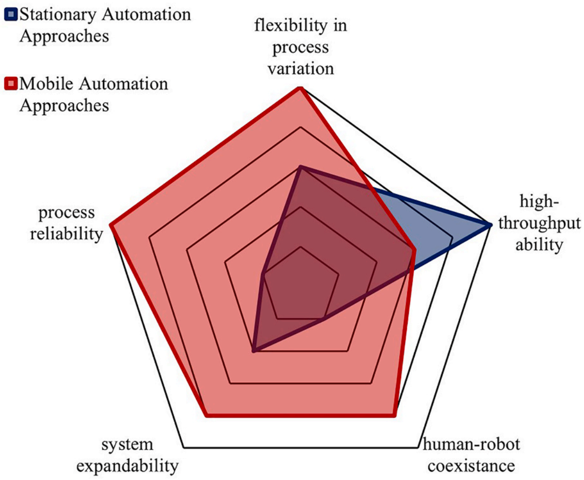

Fig. 11. Comparison of stationary and mobile automation approaches according to flexibility in process variation, high-throughput ability, human-robot coexistence, system expandability and process reliability. The outermost radius corresponds to the highest value of a property while the innermost radius corresponds to the lowest value. Stationary approaches score with high-throughput ability compared to mobile systems. In contrast mobile approaches enable human-robot coexistence, a higher flexibility in process variation, an increased system expandability and a higher process reliability.

laboratories. *Kevin* consists of the mobile platform of the service robot *Care-o-Bot* [103] and the SCARA robotic manipulator from the company *Precise*. Other than stationary systems [18,101,102], *Kevin* is developed to work in the available infrastructure of life science laboratories. The aim is to operate existing laboratory equipment and to function as external mechanical interface between the individual devices. *Kevin* is limited to the handling of well plate formats (SBS formats) which are predominantly handled in these devices. As mobile external mechanical interface for plate transports the robot is not only able to connect individual devices but also larger stationary automation systems. Concerning the overall software architecture no defined automation workflow using *Kevin* is discussed by the authors. It is only mentioned that *Kevin* is aimed to be implemented with a standardized software interface to be able to integrate the robot in any foreign control system [16]. From a user perspective, this means that no workaround such as a specific device driver is required for integration.

A more flexible mobile solution for holistic laboratory automation is represented with the *mobile robot chemist* [15]. The robot performs a holistic photocatalysis reaction workflow operating several stations in a laboratory. It is built out of a *Kuka Mobile Platform (KMP)* and a seven-axis *Kuka Leichtbauroboter intelligent industrial work assistant (LBR iwa)* robotic arm. The *mobile robot chemist* is capable of handling various container types and operates different stations with different devices like for example the *Mettler Toledo Quantos* (today: *Mettler Toledo XPR Automated Balance* [66]) solid dispenser. Concerning the software architecture of the workflow, the various laboratory devices and the robot are controlled by an overarching control system. The devices are integrated through their variable communication interfaces [15]. A further mobile approach in addition to the above-mentioned systems comes from the company *HighRes Biosolutions Inc.* Their patents describe a mobile platform designed to move various modules within the laboratory, enabling the configuration of multiple workflows with the required modules [104–106].

Furthermore, a hybrid approach from *HighRes Biosolutions* can be assigned neither to the pure stationary systems nor to the mobile systems. This is a modular approach based on movable laboratory stations and corresponding docking units so called *MicroDocks*. The movable laboratory stations have several different laboratory devices on top wherein the *MicroDocks* offer a corresponding interface for physical attachment at a specific location as well as direct communication with the overall workflow. The modularity of this approach enables flexible and fast workflow modifications. A common use case for the system is for example that multiple *MicroDocks* can be ordered around a robotic arm, and different movable laboratory stations can be docked. Through the mechanical and control technical interface a rapid and simple integration to depict various automated workflows is possible. In combination with their orchestration software *Cellario*, the company provides a comprehensive automation solution that encompasses both hardware and software. However, device integration is achieved through device-specific drivers for each instrument incorporated into the control software, thereby adhering to a workaround approach necessitated by the proprietary interfaces of individual vendors [107–109].

In summary, mobile approaches utilizing AMRs are capable of independent movement and can be implemented within existing environments, making them well-suited for human-robot coexistence. In contrast, this causes a lower high-throughput ability compared to stationary systems, as the AMR has to travel longer distances to operate the individual devices. Stationary systems have an increased high-throughput ability due to their segregated environment. In such systems individual instruments can usually only be operated by integrated robots preventing human-robot coexistence. The separate, typically enclosed environment often lacks system expandability and thereby flexibility in process variation when compared to a mobile solution. Here there is often more space to subsequently integrate additional laboratory equipment into the system and to flexibly automate further processes. Regarding process reliability, the mobile approach can be considered to have a higher process reliability, as the laboratory can continue to be operated by humans if the automated system fails. In contrast, if the stationary enclosed system fails, the process stops until the system is running again (Fig. 11).

After comparing the two methods, an assignment to the corresponding suitable use cases can be performed. Stationary solutions are particularly suitable for use in the life science sector due to their high-throughput ability and low flexibility in process variation. This includes applications in which a process is carried out numerous times and only small changes in the input parameters are repeatedly made. For example, during lead discovery, sequencing and assay development in research and development. In contrast, mobile solutions are primarily for applications in areas that are not about high-throughput but rather about flexibility in process variation. This includes, above all, supporting workflows during production and quality control such as buffer preparation, analytical measurements, small-scale filling or preparation of dilution series.

2.5. Progress of plug-and-play functionality

Advances in software and hardware technologies continue to pave the way to plug-and-play laboratory automation. Especially, extending digitalization approaches support the implementation of automation. Corresponding software solutions such as ELN or LIMS enable the digital storage and management of data. Additionally, automated hardware components, as described in Section 2.3, already enable extensive automated execution of basic laboratory operations. The development of standardized communication protocols such as SiLA, OPC UA LADS and MTP facilitates the standardization of various, individual and proprietary interface protocols deployed by vendors, thereby simplifying device integration. Nevertheless, the absence of these standardized communication interfaces in the default device configuration provided by vendors hinders their establishment. As seen for the different presented holistic workflow automation approaches in Section 2.4, standardization still mostly occurs from the user side when integrating several devices. Therefore, lacking standardized communication interfaces from vendor perspective hamper the progress of plug-and-play laboratory automation for the user. More approaches like the mobile robot *Kevin* [16] offering a standardized communication protocol already with the robot, preferably according to the SiLA, OPC UA LADS or MTP, standard are of great interest for the laboratory automation field.

From the hardware perspective several external mechanical interface technologies such as Cartesian systems, multiple-axis- and dual-arm robotic systems, and AMRs already enable robust preconditions for plug-and-play laboratory automation. However, internal mechanical interfaces at the hardware devices themselves still leave some optimization potential. Particularly, for the loading and unloading of devices like photometers and HPLC's integration of self-opening doors for example would facilitate robotic operation of such analytical devices.

3. Future perspectives

There is a trend indicating that hardware automation approaches are more advanced in the high-throughput application field than the non-high-throughput, more preparative, on-demand chemistry field. This is particularly evident in the standalone systems already available on the market. For example, liquid handler platforms such as the ones from *Hamilton Company* and *Tecan Group Ltd.* offer a great variety of integrated automated devices. Thus, there is a need for more flexible automation approaches in the preparative, on-demand chemistry field. Particularly, the ability to handle a greater variety of container types beyond well plates and tubes would be highly beneficial. This includes the handling of bottles, flasks, beakers, funnels, cuvettes and magnetic stirring bars among others. Finally, more flexible processes such as buffer or eluent preparation, dilution series preparation, or the performance of analytical measurements on HPLC and photometer could be automated. External mechanical interfaces like mobile manipulators in particular offer a wide range of possibilities for holistic laboratory automation in the non-high-throughput field.

4. Conclusion

In this review we structure the current state of laboratory automation comprising software and hardware infrastructure with respect to holistic workflow automation possibilities. We provide an insight into the basic software and hardware infrastructure required for non-application specific laboratory automation. With regard to the goal of plug-and-play laboratory automation and the resulting reduction of integration time and costs, the current state of the art, including existing technologies and approaches, is elaborated. Missing links are traced back to insufficient internal mechanical interfaces and control interfaces at the hardware devices caused by the device manufacturers.

CRediT authorship contribution statement

Aziza El Hariry: Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Maxim Polomoshnov:** Writing – review & editing, Methodology, Conceptualization. **Joaquin Eduardo Urrutia Gómez:** Writing – review & editing, Methodology, Conceptualization. **Felix Zellner:** Writing – review & editing, Conceptualization. **Rüdiger Bauer:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Adrian O'Hea:** Writing – review & editing, Funding acquisition, Conceptualization. **Kolja A. Bartscherer:** Writing – review & editing, Funding acquisition, Conceptualization. **Markus Reischl:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Ethics declaration

Review and/or approval by an ethics committee and informed consent was not needed for this study because of missing human or animal participation.

Data and code availability statement

Data included in the article/supplementary material is referenced in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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