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Industrial internet of things: What does it mean for the bioprocess industries?

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ABSTRACT

Industrial Internet of Things (IIoT) is a system of interconnected devices that, via the use of various technologies, such as soft sensors, cloud computing, data analytics, machine learning and artificial intelligence, provides real-time insight into the operations of any industrial process from product conceptualisation, process optimisation and manufacturing to the supply chain. IIoT enables wide-scope data collection and utilisation, and reduces errors, increases efficiency, and provides an improved understanding of the process in return. While this novel solution is the pillar of Industry 4.0, the inherent operational complexity of bioprocessing arising from the involvement of living systems or their components in manufacturing renders the sector a challenging one for the implementation of IIoT. A large segment of the industry comprises the manufacturing of biopharmaceuticals and advanced therapies, some of the most valuable biotechnological products available, which undergo tight regulatory evaluations and scrutinization from product conceptualisation to patient delivery. Extensive process understanding is what biopharmaceutical industry strives for, however, the complexity of transition into a new mode of operation, potential misalignment of priorities, the need for substantial investments to facilitate transition, the limitations imposed by the downtime required for transition and the essentiality of regulatory support, render it challenging for the industry to adopt IIoT solutions to integrate with biomanufacturing operations. There is currently a need for universal solutions that would streamline the implementation of IIoT and overcome the widespread reluctance observed in the sector, which will recommend accessible implementation strategies, effective employee training and offer valuable insights in return to advance any processing and manufacturing operation within their respective regulatory frameworks.

1. Introduction

In the simplest terms, Internet of Things (IoT) is a network of interconnected *things* that are able to transfer data between each other without human assistance [1]. In this context, things can be devices, machines, objects, animals or people. IoT is not a novel technology itself, but rather, it is a collection of different technologies that when combined produces a system of interconnected devices and superior analytical power.

IoT is an intricate system involving a multitude of elements (Fig. 1), which gives access to real-time data to assist sectors and companies in gaining in-depth knowledge about their business operations. IoT forms a digital system that can both make and inform correct decisions. Its true potential and capacity in various fields remains yet to be discovered with particular interest on its industrial applications. In this paper, we will outline some of the recent advances in the industrial internet of things with a specific focus on the various roadmaps and applications in the bioprocessing industry and evaluate how likely for Industrial Internet of things (IIoT) to be prominent its future.

Kevin Ashton, who coined the term Internet of Things, described the idea as:"*It (IoT) meant using the Internet to empower computers to sense the world for themselves. It still does.*" [7]. While the term was first used in 1999, the history of IoT dates back to the emergence of the internet. IoT stems from the concept of machine-to-machine (M2M), which enables machines to exchange information without human input [8]. Currently the possibilities around M2M communication are further reinforced by Machine learning (ML), which evaluates the process and makes predictions based on data collected, and artificial intelligence (AI), which helps machines make autonomous choices during operation. Most widely known or adopted recent applications of IoT range from smartphones to smart homes and smart cities. IoT devices in smart buildings range from HVAC units to motion sensors or AI cameras [9], assisting the

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monitoring of temperature to save energy, improve living standard and support sustainability in the built environment. In agricultural areas, controlling irrigation and fertilisation through appropriate implementation of sensors and processing algorithms to detect the moisture and nutrients content of the soil is another application of IoT [10]. When connected to sprinklers and weather apps, the suitable moisture content can be sustained, thus improving efficiency production; the technology has direct impact on farmers and large producers and has indirect impact on consumers of these produce.

IIoT is the utilisation of IoT technology in an industrial setting [10]. IIoT provides previously inaccessible insights to companies. The analytical power combined with the connectivity and data capabilities of cloud-computing allows enhanced interpretation of the data collected by the sensors in real-time. The concept of IIoT has particular use in the manufacturing setting and in supply chain management, where a context is given to previously overlooked data. This, in turn, results in increased efficiency, improved product quality, and prevention of potential failures through real-time monitoring and evaluation of the process.

However, at industrial level, the implementation of IoT may get more challenging than in other areas. It is not uncommon that various equipment involved in the process operate with different software rendering the implementation of an off-the-shelf solution to facilitate M2M difficult. To address this challenge, IoT platform providers offer different levels of autonomy over creating the platform based on the needs of the end user company. Whether software, platform, infrastructure or all components are required as a service, flexible solutions are offered to meet the demands of industries with processes involving multiple unit operations, each equipment acquired from different vendors, such as what is typically encountered in chemical and biochemical sectors.

With this young and emerging field creating consensus among sector leaders that IIoT will grow even stronger as we move into the future, a number of tech companies prominent in the field formed the Industrial IoT Consortium (IIC), whose goal is to facilitate accelerated implementation of the technology across all industries and to address the security issues associated with it [11].

The extent of IIoT adoption keeps growing as the benefits of connected smart devices become irrefutably clear to end users. Implementation of novel solutions, particularly in manufacturing, is associated with substantial investments and considerable machine downtime. Both are undesirable from a commercial point of view and are therefore to be avoided for as long as current solutions keep working. Furthermore, the nature of some industries such as bioprocessing renders the task increasingly complex due to additional concerns and regulations that need to be taken into consideration, as we will discuss in the following.

In the following sections, a comprehensive understanding of the terminology and components of IoT concepts will be presented, along with a discussion of the extent of progress shown by sectors in implementing IIoT solutions with a specific focus on bioprocessing industry. We identify a critical evaluation on the current state of IIoT implementation of IIoT in bioprocessing and discuss the necessary and missing components for a successful application of IIoT and present a roadmap to address current challenges and facilitate the transition into connected processes and operations in the biomanufacturing sector.

2. Search Methodology

The methodology is described in detail in this section to assist the repetition of the analysis and advise further similar research on contemporary technological advancements in a specific sector, which suffers from the availability of limited scientific literature: The literature search was conducted accessing the following online search engines: Google Scholar, PubMed, Science Direct, Wiley Online Library and IEEE XPlore Digital Library in the timeframe covering November 2022 – April

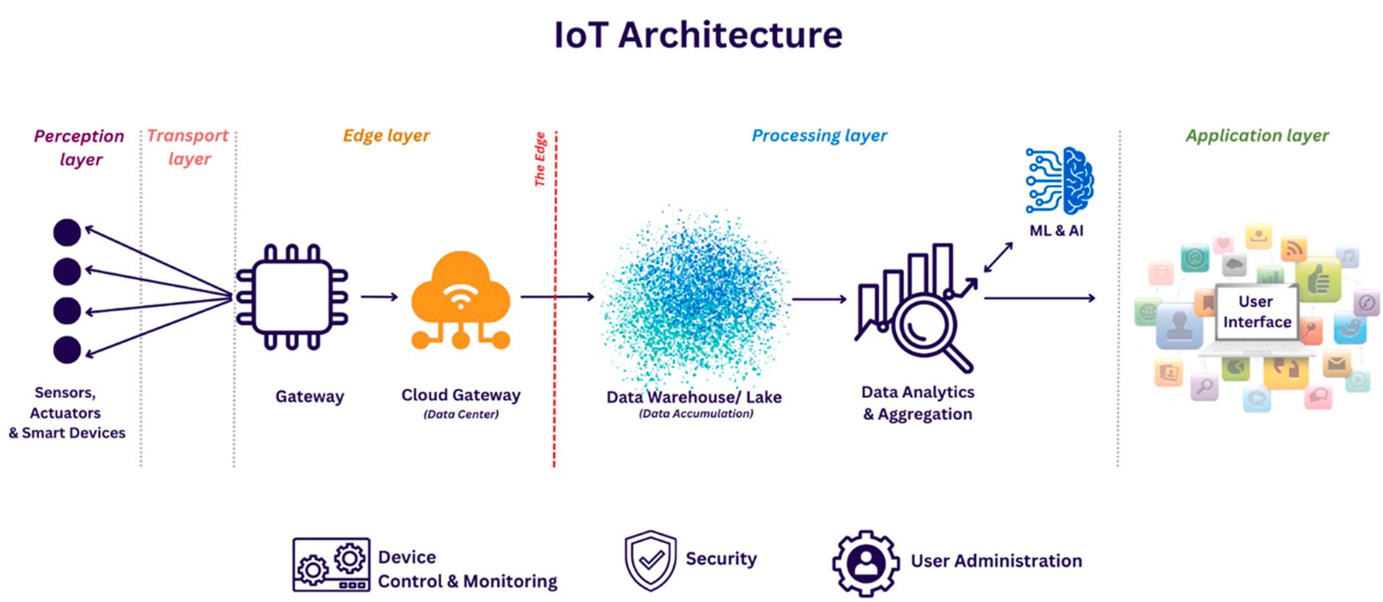

Fig. 1. IoT architecture with all different layers and its most important components. The perception layer includes : sensors, which are devices collecting the data from their environment, and actuators that are able to act on the data collected to provide an end result previously defined by the user. There are different connectivity methods besides internet including Ethernet, Bluetooth, cellular standards such as 5 G or low-power wide-area-network. Once data is collected from all sensors to a sink node, it is transferred to an IoT gateway. IoT gateways translate the analog sensor data into digital form for further deployment, and act as a communication hub for the smart devices. The data then moves onto the Cloud gateway. The devices are resource-constrained, meaning that they cannot process and analyse their own data. Beyond the 'edge' is the computing power of data analytics, machine learning, artificial intelligence and cloud data storage, but the edge layer allows for pre-processing of the data to quickly react and mitigate problems without the need for extensive analysis and computing on-device. The data is then transferred beyond the edge to data centres: cloud, data warehouse or data lake, which leads to the processing layer. Once the data is processed and interpreted, it is ready to be presented to the user [2-6]. This representation also includes the communication and information flow inherently. The industry specific ISO and ALCOA+ standards and guidelines associated with the information flow are discussed in detail in Section 3.4.

2023. The following keyword combinations were employed to conduct the search to allow the maximum possible information available to be captured during search (Table 1).

The specificity of the keywords improved during this process based on the extent of information sought after in three different components: IoT elements, different sectors of the bioprocessing industries of interest, and relevant phrases and concepts found in the primary search articles. Each different IoT element has been around for a different extent of time and the level of advancement in applications utilising a range of IIoT technologies differs in the bioprocessing industry. To accommodate for the most comprehensive search available, the keyword-based preliminary search was supplanted by further search where the criteria were expanded to include any potentially relevant secondary research articles discussed in the resources identified from the primary search (Table 2). In addition to scientific journals, website articles were also accessed, and discussions were carried out with thought leaders of the sector to understand the primary concerns and challenges. The leaders were given the same set of questions to understand varying points of view on some key aspects of IIoT, followed by open discussions (March 2023). The inclusion criterion for online resources was the mentioning of IoT or its elements being utilised in any operation within the industry. Some sources misreferred to the terms IoT or Industry 4.0 in a discussion around automation or digitalisation, which were excluded from further evaluation. If the attribution to IoT concepts was too general in the resource, if IoT was defined incorrectly or was only minimally discussed, the resource was excluded. The inclusion criterion for example applications was for the application to include at least one element of an IoT system applied to any area of operation within a company or a study representing how it can be applied to an industrial bioprocess. The scope was kept broad including standalone component applications in addition to full-out IoT applications in the bioprocess industry due to the limited number of full-out IIoT applications in bioprocess industries.

For each online resource, the aim was to extract the relevant data to address the following:

Table 1
Different keyword combinations used to extract information from the search engines*.

No.	Keywords Combinations Searched For Simultaneously
1	IoT/Internet of Things and Bioprocessing/Bioprocess
2	Industry 4.0 and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
3	Digitalisation/Automation/Automatization and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
4	Digital Twins/Artificial Intelligence/Machine Learning and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
5	Soft Sensors/In-line Sensors/Software Sensors and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
6	Smart Management/Supply Chain Management and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
7	Analytical Methods/Analytical Technology and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
8	Hybrid models/Hybrid modelling and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
9	Process Development/Design and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
10	Monitoring/Control/Real-time Monitoring and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
11	Application of IoT/Implementation of IoT and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
12	Regulations of IoT/Data Integrity and Bioprocessing/Bioprocess/Biopharmaceutical/Pharmaceutical
13	EMA/FDA and IoT/Internet of Things

* *The words before and after "and" were searched together. Only two words or phrases were used in search together at any time. The "/" denotes an OR relationship where either word or phrase was used in conjunction with another word or phrase following 'and'.*

Table 2
Number of references selected for each category of different areas of applications evaluated in the article.

IoT element / Area of operation/ Type of application	Breakdown of the total number of. references selected for each category
Internet of Things	15
Industry 4.0 (incl. PAT, DoE, MVDA, PCA, ML & QbD)	13
Digitalisation	1
Digital Twins	7
Soft Sensors	12
Process Monitoring	6
Hybrid Modelling	4
Regulatory & Safety Concerns Surrounding IIoT in Bioprocessing	9
Challenges Faced by IIoT in Bioprocessing	5

- Identify the specific process stage in which the IIoT application is employed (e.g., process design and development, manufacturing, supply chain, human resource management, resource tracking).
- Determine whether the discussed application was a theoretical exercise or has been challenged in real-life conditions.
- Determine whether the case discussed is a full-out IoT system implementation or an application of one or more elements of IoT, and if the latter, also to identify which IoT system elements were utilised.
- Determine the extent of IoT application, whether that be focused on a limited number of equipment and machines or demonstrate a system-wide operation.

The collected information was then categorized based on the IoT element it concerned, the area of operation or the type of application it concerned.

3. Current state of art of IIoT in bioprocessing

3.1. Current tools, approaches and initiatives leading towards adopting Industry 4.0

Industry 4.0 aims to employ digitalisation, the concept of cyber physical systems (CPSs) and IoT in the processes that were proposed to be automated within the scope of Industry 3.0 using logic processors and information technology [12]. In the context of bioprocessing, this opens up a new dimension of potential improvement in productivity, flexibility and control, with the end goal of creating smart biomanufacturing plants with a wide web of interconnected devices with a multitude of benefits (Fig. 2) [12–17].

Bioprocessing practices, especially in the biopharmaceutical sector, were highly heterogeneous with regards to digital transformation, with some leading the advancement and acting as flagship operations whereas other practices remain to fulfil the standards expected of the Industry 3.0 transition. Digitised data collection remains a goal to be achieved completely, and this reluctance renders the operation prone to human-error and limits the possibilities around data utilisation [2,12]. Currently, adoption of digital technologies appears to be more widely accepted in upstream bioprocessing than in downstream bioprocessing [2]. Automation in downstream unit operations is incomplete, which renders interconnectivity difficult, and the limitation in the number of in-line sensors restricts the volume of data collected, which prevents powerful control strategies based on soft sensors to be developed. Employing Industry 4.0 solutions, such as process analytical technology (PAT), design-of-experiments (DoE) and multivariate data analysis (MVDA), were proposed to resolve issues associated with the ease of connection and data collection, while increasing efficiency and minimising the uncertainty caused by human intervention [12].

Digitalisation maximises the capabilities of people, machines, and

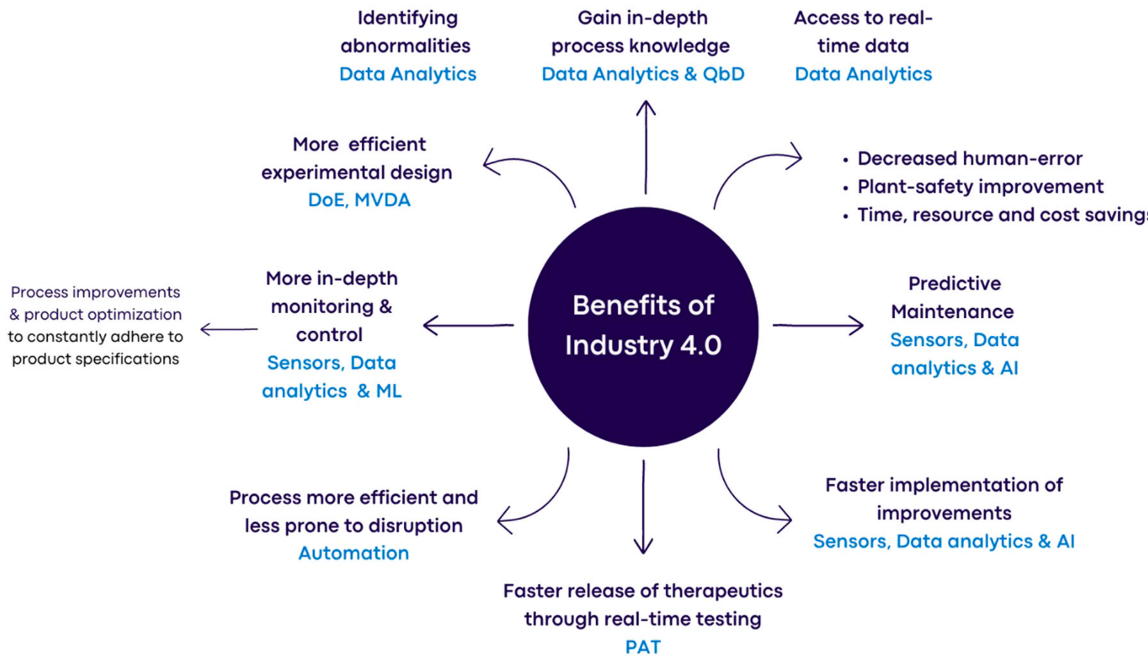

Fig. 2. Benefits of Industry 4.0 for bioprocessing. Bioprocessing integrates organisms or cells, such as microbial, algal, animal or plant, or their parts to manufacture a variety of different products from pharmaceuticals and foods to chemicals and biofuels [18,19]. However, the involvement of biological systems in production amplifies the complexity of the process. Therefore, implementing novel solutions means higher risk and greater investment, rendering numerous potential benefits of Industry 4.0 to advise, guide and support these decisions renders the strategy even more valuable.

the data collected by introducing analytics and connectivity, which, in turn, yields facilities with increased flexibility and productivity [20]. IoT takes this notion one step further and aims to create a holistic view of the past, the present and the future, through analytics and predictions, which enables the response to be proactive, rather than reactive to events. Different tools and initiatives prominent in the domain of Industry 4.0 enable some extent of progress leading towards the implementation of IoT (Table 2). While these methods have been employed for a number of years, they have been adopted with the primary incentive to extract information that yields a superior understanding of the process operations, but not with an end goal to modify the process as a whole to improve outcomes.

Quality-by-Design (QbD) and PAT have been around for at least 20 years following the introduction of these concepts by the Food and Drug Administration (FDA) and later being endorsed by the European Medicines Agency (EMA) [12,21,22]. These initiatives and those that follow aim to improve the pharmaceutical production processes through the adoption of new technologies; the implementation of QbD itself provided multiple benefits to the industry, similar to those provided by Industry 4.0, such as improved process understanding, while the PAT initiative aims to push it even further towards real-time monitoring of processes.

Regulatory bodies have supported transitions towards making better informed decisions to design and implement safer processes than their predecessors for decades, and this overarching goal is well-aligned with the objectives of Industry 4.0. Despite being first introduced more than two decades ago, the challenges around these goals remain very contemporary; the aims and the priorities of the sector remained similar with product safety and efficacy being the top concerns. What is interesting to observe is that the technological objectives also remained very similar over the course of these past two decades. The initiatives and solutions discussed in this section paved way towards the exploration of next generation techniques and approaches such as soft sensors, hybrid modelling, digital twins, and ML, which are directly associated with the concept of IIoT. Both QbD and PAT initiatives iterate the need for the development of soft sensors to address the issues around process variability and the need for advanced schemes for monitoring and control in development and production, all of which will be discussed in the following.

3.2. *Current practice: IIoT applications in bioprocessing*

Industry 4.0 aims to transform traditional ways of manufacturing and industrial processes through automation, digitalization, data analytics, connectivity and implementation of CPSs. Embodying all these elements, IIoT has the potential to boost industrial operations. Despite the complexity of this task, examples either of one or several elements, or full-out applications in bioprocessing are available (Table 3). .

In one of the pioneering soft sensors application, Warth et al. monitored a fluorescent protein expressed in *E. coli* in a fed-batch culture [25]. The absorption of the expressed protein was measured by a probe and the signal was then processed through an algorithm to infer the growth rate and the glucose uptake rate of the microbial cell culture. Soft sensor estimators and other soft sensor applications have been around for more than two decades and their utility has been justified repeatedly, especially in the domain of process monitoring and control, wide adoption of the technology could not yet have been achieved [40]. An example application of IoT elements in the model predictive control and Quality-by-Control domain was demonstrated by a simulation run in the Novartis-MIT centre as a plant-wide control strategy [27]. The application also demonstrated the power of PAT technology in process control, performance and stabilization.

Automated upstream process development that utilised DoE on benchtop bioreactors were rendered feasible and resource-wise manageable through the micro bioreactor system originally designed by The Automation Partnership (TAP) [29]. The utility, reliability and the performance of such systems were evaluated by leading biotherapeutics manufacturers [29,30]. Automated scale-down mini bioreactors assist transition towards Industry 4.0 since they offer a route for speeding up process development and allowing better-informed decisions to be made at very early steps in the process when coupled with rational modelling approaches. Legacy data can be beneficial to gain

Table 3
Common Industry 4.0 tools, initiatives and approaches that facilitate IoT transition and their role in the context of bioprocessing.

Tool/ Initiative		Role in Bioprocessing
QbD	Quality by Design	Strategy for designing, analysing, and controlling manufacturing through in-process measurements of critical quality attributes (CQAs) and critical process parameters (CPPs) to ensure final product quality[14]
PAT	Process Analytical Technologies	Real-time process control techniques ensuring final product quality through online process monitoring[21]
DoE	Design of Experiments	"Approach that involves systematic and efficient examination of multiple variables simultaneously to create an empirical model that correlates the process responses to the various factors"[23]
MVDA	Multivariate Data Analysis	Allows to analyse multiple variables at once, establishes correlations between them, and overcome challenges such as missing data and variations by means of projection methods such as PCA, PLS and multiple regression[24]
PCA	Principal Component Analysis	Reduces a number of components for analysis by summarising the data into fewer new variables known as principal components[24]
ML	Machine Learning	Aimed at "finding suitable, mostly empirical models to describe datasets, learning from labeled samples or by identifying inherent patterns"[13]

in-depth understanding of a system, and in turn, impact various decisions associated with production. Narayanan et al. employed historical data from 81 fed-batch CHO cell cultures to develop a hybrid model that estimates unknown uptake and secretion rates in a fed-batch CHO cell culture [35].

IoT implementations not only offer solutions for process development and manufacturing, but also, for the whole lifecycle of the product, including its delivery to the end user. In the context of biopharmaceuticals, product sensitivity to environmental conditions during transport necessitates consistent and proactive control of the supply chain. Amgen's software platform Supplier Relationship Excellence allows for data exchange with suppliers of raw materials, and uses predictive modelling to manage demand, identify potential improvements in the chain, and ensure sustained quality of products [32].

These example applications of IIoT elements do not necessarily convey the true potential of an IIoT system, which could only be demonstrated by full-out applications. An example full-IoT system in bioprocessing is described from Sanofi's Massachusetts manufacturing facility. It is reported to employ multiple elements of IoT infrastructure from digitalisation and closed-loop controls, through digital twins and sensors to cloud-computing and real-time process monitoring [39]. Sanofi recognizes the benefits such solutions can bring to their continuous biologics production and employ them both in upstream and downstream bioprocessing. This platform was reported to generate five billion data points per batch from over 5000 parameters that were monitored through multiple in-line sensors [39]. This reinforces the notion that process monitoring where data is collected at this scale and rate would not be possible, feasible, nor broadly useful without implementation of digitalisation and ultimately IoT. Sanofi acknowledges the need for employee training and support for such a transition at scale, and provides integrated quality laboratories and augmented reality-driven training. The scale of the transition was reported to come at a cost where €4.7bn investment was made over the course of 5 years and plans were already in place to invest €600 m per year to support this initiative and digitalise other facilities in the future [39].

Brewing industry embraces full-out IIoT system applications more extensively than biopharmaceuticals and advanced therapies space. IoT can be employed at every stage of beer manufacturing from milling, through fermentation to packaging [41]. Smart Creek Brewing is among those producers who took advantage of implementing both cloud based IoT and AI solutions to improve product quality [38]. Albrlgi Beer reported adopting a smart brewery system where the mashing and wort boiling phases of the process are fully self-managed [38]. IBM or AB InBev announced that they provide solutions for smart beer production to support and widen the participation in this sub-sector.

Table 4
Some IIoT applications in bioprocessing found during search [25–39].

Tool/Approach	Details	No. reference
Soft Sensors	Estimation of growth rate and glucose uptake based on online, in-situ measurements in E. Coli fed-batch culture	[25]
	Prediction of biomass, viscosity and production for better control and automation of penicillin production	[26]
Model Predictive Control (MPC)/ QbC	PAT technology and MPC as a plant-wide control strategy	[27]
Digital Twins	300 engines integrate to supply historical and real-time process information for predicting process failure, mitigating risks, and optimizing maintenance costs	[28]
Predictions	High-throughput automated scale-down bioreactor mimic These mini bioreactors have been shown to provide robust estimates of process performance and product quality from bench to pilot scale	[29,30]
	On-line estimation of biomass, glucose and ethanol in Saccharomyces cerevisiae cultivations	[31]
Process Monitoring	Supply Chain monitoring for ensuring consistent biologics quality using feedback loop from electronic data and predictive models to anticipate supply issues or identify any improvements	[32]
	Process monitoring software platform for real-time monitoring of quality attributes (Use of MVDA ad PLS)	[33]
	In-line Raman Spectroscopy used as an automated online method to measure multiple analytes simultaneously in mini bioreactors and to rapidly and more easily build models that can control their bioreactors	[34]
Hybrid Modelling	Hybrid model for estimates of key nutrient/ metabolite concentrations in fed-batch CHO cell culture	[35]
	Hybrid modelling for prediction of duration of cross-flow ultrafiltration processes and flux in batch and fed-batch models for concentration processes	[36]
	Hybrid modelling platform to estimate mAb glycosylation profiles by using intracellular	[37]
Full-out IIoT System	Photos of beer interpreted by an algorithm in the cloud to elevate the quality of beer manifolds Self-managed mashing and wort-boiling phases	[38]
	Digitalization, Cloud-computing and digital twins implementation in biopharmaceutical Sanofi plant in Framingham, Massachusetts.	[39]

Merck Millipore Sigma invests in IIoT solutions that are not directly related to biomanufacturing but rather lie in the domain of provision of auxiliary services [42,43]. They developed an IoT platform of a production plant in Darmstadt, Germany that provides mobile accessibility to all employees. This system was equipped with numerous sensors for predictive maintenance of plant equipment and devices.

It should be noted that despite the reporting of the monetary investment made to refurbish an existing operation to comply with IIoT, no systematic economic or technoeconomic analysis has been carried out to investigate the implementation of an IoT system for bioprocess industries as a generic exercise. Therefore, we do not currently possess information on how the implementation of an IIoT-compliant operation and its subsequent use would reflect on operating and capital costs. The limitations and challenges associated with full-out IIoT applications stem not only from the substantial costs associated with the process, but as mentioned earlier, also because of concerns around regulation and security aspects. We cannot rule out the possibility that at the time of this evaluation, there are ongoing efforts yet not shared with the bioprocessing community. Since there are no established solutions, each application will remain unique with their cognate strengths and thus could potentially serve as background IP for the commercial setting that they belong to.

IoT is a broad concept that is often interpreted in various different ways. Exiting literature offers different explanations as to its meaning and definition, and is often interchangeably or even synonymously used with one or more of its elements or concepts such as digitalisation, automation or data analytics [44]. In line with this notion, currently no consensus understanding or definition of IIoT is available for bioprocessing industries either. Discussions carried out with experts from the bioprocessing research community were very helpful at this stage to evaluate the current perception of the technology in the context of bioprocessing and biomanufacturing.

All experts, regardless of their familiarity with the concept, sought to agree on a universal definition of IoT before getting into the discussion. One expert emphasised the importance of this by stating that definitions bring along preconceptions. Breaking IoT down into separate subconcepts may encourage potential users of the technology towards new solutions because they are more straightforward and do not carry as many unknowns.

Another issue to be taken into consideration by the industry is the presence of strict regulations that may potentially serve as a limitation for the implementation of novel technologies since they are not covered by the regulations. This is a perceived risk working against the implementation of IoT by the bioprocessing industry. Even though there are other highly regulated industries, such as banking or aviation, where IoT applications are thriving [45,46], the difference is in what is actually regulated. Both the process of production and the quality of the product are regulated in the bioprocessing industry. Once the process for manufacturing the product is developed, the process and product safety, efficacy and quality are evaluated in costly clinical trials. One of our experts addressed this point by highlighting the low success rate of clinical trials and pointed us to the dilemma around the clinical trials and process from which the products used in the trials arise: The process, being the basis for the clinical trials is fixed and no longer changed once the product gets into trials. Even if an intervention may improve the process, any such change would imply that the clinical trials would have to be reinitiated, so this option is not explored. Regulators recommend the innovation to be designed into the process, which is aimed to be addressed by the QbD approach. There are currently no available off-the-shelf IoT solutions for the industry, and development of customized applications is costly. The high failure rates in clinical trials disincentivises the development of these resource-intensive tailored solutions for each candidate product/process. Another expert explores what this would mean for successful candidates that make it to market and points out the fact that it would be unlikely to implement new technologies at that stage either, since this would implicate the need for re-patenting of the product which would be costly, and delay the time to market. The need for revalidation or potential loss of IP rights in the event of any modification of the process that would render the product no longer patent-protected remains one of the biggest concerns of the industry.

Although studies have shown that digital technology improves production efficiency by 30–35% [17], productivity does not rank high on the list of priorities in the bioindustry of medicines and advanced therapies. Our experts bring this to attention by stating that acquiring the regulatory approvals and getting the product to market first is the overriding driver, but having the most efficient process has not been the biggest largest business driver for biopharmaceutical and advanced therapies processing. They further reinforce this by stating that the industry is already undertaking big risks in bringing the product through clinical trials to the market and the primary point of concern is security, particularly in such an IP-intensive industry as biomanufacturing of medicines.

Experts who contributed to this discussion also pointed out the challenges around the complexity of the process, not only associated with the biological systems or parts, but also arising from the diversity of the equipment and software employed in different unit operations of the process. Compatibility is pointed out as one of the main issues by all experts. They pointed out the need for an intermediate software or programming language that analyses the results from one operation and then talks to the other to facilitate communication for further analysis. Experts also acknowledged Allotrope Foundation as a platform that offers a standardised framework to obtain uniform data and minimise data loss [47]. They stated that adopting this kind of standardisation would make it easier to implement solutions such as IoT. Furthermore, it was acknowledged that not all operations in bioprocesses are very suitable for an automated integration, or at-line measurements utilising smart sensors. Some offline sampling and analytics such as gel-based separation and product quality verification methods can be more difficult to integrate into an IIoT platform than others.

All experts agree that there is room for improvement in utilising the available data in bioindustry. The main obstacle is perceived as the limitations around the underlying infrastructure for the implementation of IIoT. One expert pointed out that validation is often carried out using non-digital platforms, i.e., paper even in this age of digitisation. Bioprocessing industry suffers, at times, from not complying with all standards of Industry 3.0, with some companies only recently starting to employ solutions that have been available for decades. To reinforce this notion further, one expert referred to bioprocess industry as one of the lowest-tech industries in the world, that produces some one of the most valued products. Some solutions that have been around for decades are speculated to be used by only 1–2% of the biomanufacturing operations. Experts formed a consensus around mentioning the bioindustry's reluctance and pace to adapt changes even before IoT solutions and the cognate modifications in infrastructure could be considered.

Expert reiterate concerns around security that by allowing connectivity of all systems and company-wide access, particularly in manufacturing, the organisations may experience risking the proprietary information breaches and cyber-attacks. Some offer closed-loop systems with a centralized data hub as a possible solution to alleviate the risks, while others reflect on the weak spots around current practices such as the use of unsecured USB sticks and Excel sheets to transfer data and the concerns around IoT less prominent than those.

We observe that some reluctance and concerns around IIoT in bioprocessing arise from lack of understanding and sufficient knowledge, and this serves as a substantial industry blocker (Fig. 4). Industry 4.0 enables faster development, higher efficiency and process understanding. Experts agree that IIoT will eventually become a key part of the bioprocessing industry, however, they do not consider this likely in the immediate future, as it will heavily rely on improvements in cognate domains until its adoption by the industry.

3.3. *Monitoring and control using next generation IIoT technologies: soft sensors, hybrid modelling, machine intelligence, and digital twins*

A dependable bioprocess control strategy monitors critical process parameters (CPPs), ensures that the relevant product specifications are met, detects unexpected behaviour and deviations emerging in the process and takes the relevant control actions. The capabilities of smart devices within the manufacturing process, such as soft sensors, are not limited to measuring process parameters but also tracking and tracing the data they collect, detecting abnormalities and assessing the health of equipment and instruments in real-time. When combined with powerful analytics, edge and cloud computing, ML and AI, soft sensors can be very powerful not only to develop next generation control strategies, but also to improve the process in real-time [48]. An integrated IoT system comprised of these elements can be very beneficial in complex manufacturing settings such as those encountered in bioprocessing. However, the application of full-out IoT systems is not common. Only parts or specific elements of full-out IoT solutions are employed for various reasons ranging from the high costs and complexity associated with a full-out implementation, to reluctance arising from regulatory and security concerns.

Sensors are the starting point of an IoT system and a key to process control. They act as a data collection sink, which can later be analysed and used by both the equipment and devices integrated within the process and the users overseeing the operation. Unlike their predecessors, the hard sensors, soft sensors are not only used to measure the data but also take part in storage and predictive model design. They employ the power of mathematical models to allow the users to monitor CPPs in real time [49,50]. Reliable soft sensors constitute a key requirement for the effective implementation of novel solutions such as IIoT, PAT and other monitoring approaches (29).

Model-driven soft sensor applications, often referred to as first principle models, are based on the biological, chemical and physical principles, and they attempt to provide a complete understanding of the underlying process [49,51,52]. They are focussed on describing the ideal process conditions, and therefore they are primarily employed in process development, particularly in the optimisation of upstream bioprocessing [40,53,54]. Data-driven soft sensors function solely based on observations of the process, with example applications encountered in monitoring of data for cell density, nutrient concentration and product quality in monoclonal antibody manufacturing [48]. MVDA is typically employed to relate the CPPs to CQAs, while PCA and partial least squares (PLS) are frequently used as black-box modelling techniques [49].

Hybrid models, also known as grey-box models, merge the benefits of mechanistic model principles and system outputs [51]. Hybrid modelling offers the possibility to shorten the development time and reduce cost, especially when combined with Design of Experiments (DoE) [51]. Improved understanding of the process reduces the number of experiments required for process development hence decreasing associated time requirements and cost. Broadly speaking, hybrid modelling has the potential to realise some of the Industry 4.0 objectives such as model-based control [55] and process optimisation to enhance product quality [37].

There are different application domains for these next generation technologies in various domains including, but not limited to the prediction of process variables, process monitoring, anomaly detection and predictive maintenance, and supply chain monitoring.

By leveraging machine learning techniques, soft sensors enable prediction or estimation of parameters that are difficult to measure based on other CPPs [40]. Such predictions are the original and currently the most prominent area of implementation for soft sensors [49]. This approach expands process knowledge particularly about the variables that are directly or indirectly related to the quality of the final product. It is easier to build in soft sensors into the control loops of established automated processes, which is not often encountered in biomanufacturing. Consequently, soft sensor applications have shown promise in research and pilot-scale applications but are mostly theoretical and not widely adopted in commercial manufacturing settings [56].

Another area of application that utilises soft sensors is monitoring and fault detection, both in the processed and the devices and equipment themselves [49]. Analysis of the sensor-generated data can be used to detect anomalies in real-time and trigger alarm signals or instigate corrective actions. Combined with machine learning, it can produce algorithms based on historical and real-time data to detect process deviations at an early stage and overall improve process control performance. Moreover, this capability may allow predictive maintenance of machines, which leads to decreased downtime and potentially to reduced costs, since repair can be scheduled in advance, prior to actual machine failure [57]. Considering that high operating costs are observed in the bioprocessing industry, such soft sensor applications offer to bring multiple benefits, although it is still difficult to evaluate the true impact of these sensors in predictive maintenance since many proposed discussions are currently stalled at the level of conceptualisation.

Supply chain control is crucial as handling products sensitive to the outside conditions calls for reliable monitoring to ensure prescribed conditions during transport. Wireless soft sensors can be used to monitor environmental conditions as the collected data can be evaluated via quality degradation algorithms in the cloud database [58]. The World Health Organization reports global vaccine wastage of up to 50% on an annual basis, largely due to a lack of temperature control and the logistics to support an unbroken cold-chain [59]. In many instances, the wastage of bioactives such as vaccines or biotherapeutics not only implies loss of an investment, but also a delay in treatment. IIoT, through AI-informed predictive modelling, can offer a partial solution to this problem, since increased knowledge about the supply process can help adjust or even formulate ways for improved supply chain management.

Digital twins are virtual models that reflect an actual material object or its behaviour as closely as possible [60]. In manufacturing, they are virtual representations of production systems that mirror the behaviour of system parts and their relationships [28]. The virtual models are defined as a collection of previously collected and real-time data, as well as any defined process conditions that are not deduced directly from the software. During process development, digital twins allow to simulate the process, test its feasibility and predict potential risks and system weaknesses, while during manufacturing they support the optimisation of the established process and assist data analysis [28]. In bioprocessing, digital twins can be used to create dynamic models to predict process parameters based on whole process data, and to enhance process understanding through simulations. Simulations can advise system behaviour in extreme scenarios, which would allow countermeasures to be developed in advance. The most important aspect of digital twins constitutes the integration between the virtual and physical systems.

Various solutions are available to facilitate integration between virtual and physical spaces through IoT service platforms, such as Mindsphere from Siemens or Predix by GE [28]. These solutions provide users the opportunity to design the visualisation of their system, analyse and manage the data via the cloud, which is one of the key components of any IoT system. Other platforms such as Amazon, Microsoft, Google and IBM also offer data management solutions with analytical tools to enhance the implementation of IoT in an industrial setting.

Despite meticulous efforts of IoT platform providers to ensure that their service on offer is as efficient and secure as possible, the lack of standardised frameworks and data formats, ceases the progress towards Industry 4.0 [28] in many sectors including bioprocessing. Lack of compatibility between equipment in each unit operation hinders the feasible implementation of digital twins and other IoT solutions. Digital twins offer in-depth process insights, improved control over the process and superior efficiency. However, as in the case of soft sensors, the available offers in bioprocessing are predominantly theoretical at the moment, and are difficult to implement in biomanufacturing, although they prove quite useful in the process development stage [61–63].

3.4. Regulatory and security considerations surrounding implementation of IIoT in bioprocessing

Bioprocessing industry is a subject to strict regulations to ensure safety and quality of products. Not only the manufacturing of biopharmaceuticals and advanced therapies, but also other bioproducts such as foods, specialty and commodity chemicals and biofuels also have to meet predefined quality criteria to override the potential inherent variability introduced by the utilisation of living organisms or their parts as manufacturing hosts. Some of the key regulatory concerns are addressed through (i) Good Manufacturing Practices (GMPs), which constitutes a set of regulations aimed at ensuring consistent production that is up to predefined quality standards [64], (ii) process validation, (iii) quality monitoring and control, (iv) risk management, and (v) health and safety practices, including those that concern the handling of biohazardous material involved in bioprocessing.

These regulatory action points all aim to reinforce the absolute requirement of consistency and safety in biomanufacturing, but they may, at the same time, impose limitations on the extent of IIoT onboarding, especially from a the manufacturing standpoint limiting the implementation of IIoT solutions in bioprocessing very scarce [64]. An example of this could be seen in the implementation of AI-based strategies, for example. The concept of sustained process improvement through AI may become challenging from a process auditability point of view. On the other hand, employing IIoT solutions in quality monitoring and control suggests a huge potential for process improvement throughout the production timeframe since the implementation of superior control systems that ensure product quality more effectively renders manufacturing better compliant with GMP standards.

A regulator-driven initiative to encourage the utilisation of IIoT solutions will provide unprecedented incentive towards embracing these novel technologies more widely. While, the implementation of these solutions in process monitoring and control later on in the process is risk-averse, the regulations surrounding the biomanufacturing step are quite strict. FDA requires that the "process validation should provide scientific evidence for the safety, efficacy, and quality of the product. These criteria cannot be achieved by in-process controls or final product testing, but must be implemented into the process" [65]. This requirement inherently suggests that the implementation of IoT monitoring and control tools, such as soft sensors, hybrid modelling, digital twins or the use of AI or ML would be suitable for process development rather for an already established process that is to be utilised in manufacturing.

ISO standards addressing IoT and cloud computing exist as an overarching guideline for all industries to establish an agreed-upon understanding of the implementation standards, wireless communications and security considerations [66]. However, there are no specific ISO standards exclusively addressing IoT in bioprocessing. Instead, the regulators attempt to address this gap. One set of guidelines are summarised by the ALCOA+ principles [67]. These principles do not only address different aspects of data integrity, but also set out guidelines for both paper and electronic data (Fig. 3). .

ALCOA+ was introduced by the FDA in 2013 and is currently used across FDA, EMA and Medicines and Healthcare products Regulatory Agency (MHRA) [68]. Apart from ALCOA+ , standards are provided by other organisations to assist smart manufacturing and IIoT come to life. The International Society of Automation created an international standard for company-wide control system, the ISA 95 Framework [69]. This framework helps to standardise the communications between the different levels of an organization, and particularly for IIoT it helps to harmonize the different elements of IIoT and helps present IIOT based on an established framework [70]. Following the established guidelines such as ALCOA+ or ISA 95 supports manufacturers in implementing novel digital solutions, but the current state of the art is still far from a full-out IoT application. The available guidance specifically related to IIoT solutions is nevertheless limited, and consequently creating reluctance in application.

Data security and integrity are among critical concerns around the implementation of IIoT solutions, particularly in the context of intellectual property (IP) rights and licensing. Data breaches have serious consequences as sensors collect sensitive and valuable, often proprietary, information in bioprocessing industries. Furthermore, connecting all devices in an integrative system could potentially place the entire production at risk potentially due to hacking or due to system-wide technical failures unless necessary precautionary measures are taken.

There are some trivial security breaches or potential breaches and exposures in relation to data integrity currently experienced in the bioprocessing industries due to issues associated with existing practices. Most commonly reported violations are to be easily avoidable, but an important implication was reported to be that almost half of these could potentially jeopardize the regulatory status of an operation [47]. Most common types of violations are data manipulation and falsification, which could readily be minimised by the implementation of digital systems such as PAT, since data tempering is traceable in a digital environment. Another frequently encountered issue is the collection of incomplete data due to manual data collection practices or to the use of non-validated software. There is a consensus among the bioindustry towards the utility of digitised data collection to surpass these problems.

Many products and therapies within the biopharmaceutical sector are patented, which gives the manufacturers exclusivity to sell the product for 20 years [71]. This sector would benefit the most from the implementation of IoT solutions during the process development, which is when most often the patent is not yet granted, thus the companies intellectual property rights are most vulnerable. While the use of cloud

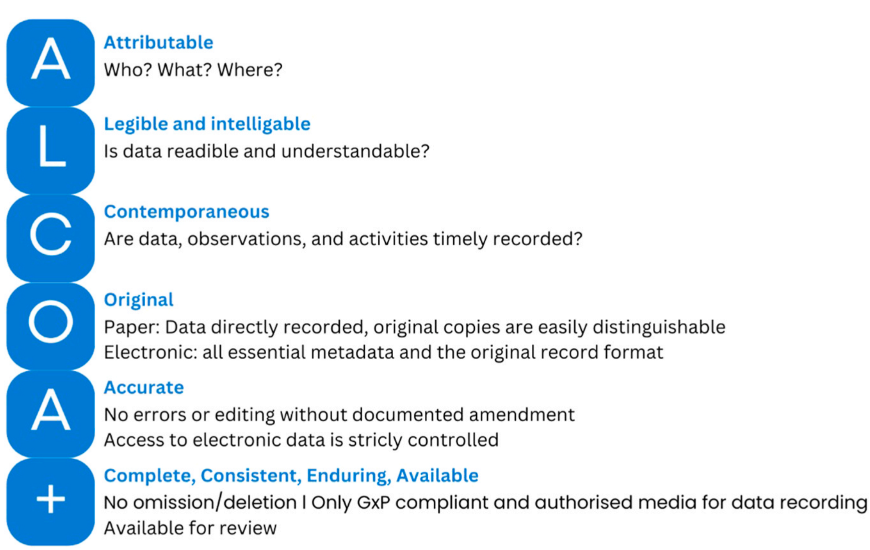

Fig. 3. Summary of the ALCOA+ Principles for data integrity. These principles summarise a guide for life sciences manufacturers to ensure that their data is attributable, legible and intelligible, contemporaneous, original, accurate, and that they ensure data also to be complete, consistent, enduring and available.

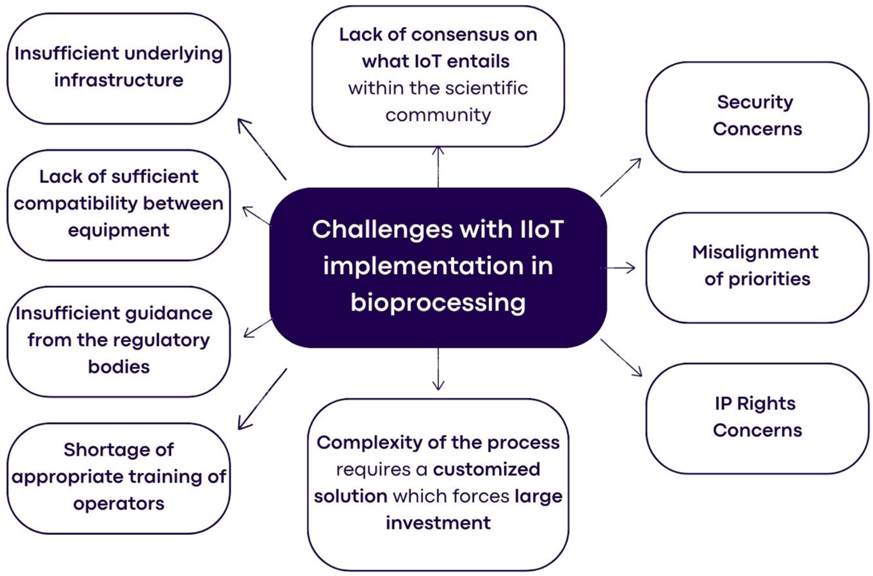

Fig. 4. Challenges associated with IIoT implementation in bioprocessing industry. A summary of the critical overview of existing literature, grey and white papers, along with expert opinions is provided here.

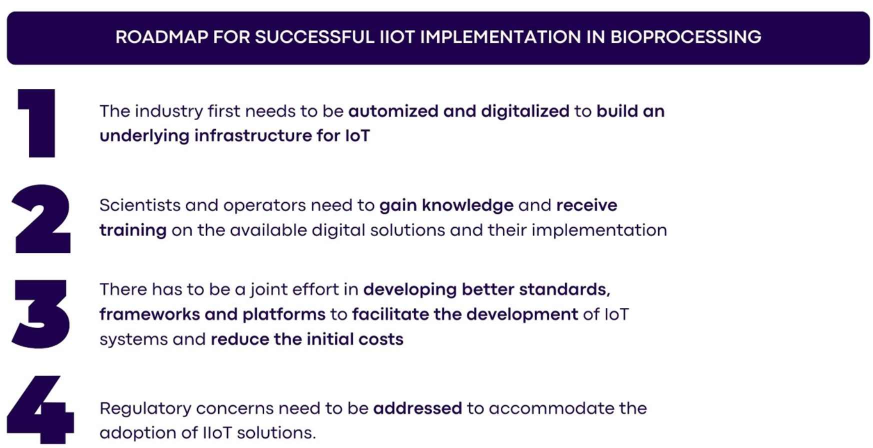

Fig. 5. Roadmap for successful IIoT implementation in bioprocessing. Steps suggested to be taken in order to achieve efficient and widely adopted implementation of IIoT in bioprocessing industry.

platforms to collect and store data has been under scrutiny for exposing the system to potential data theft, current cyber-security measures, such as two-point authentication, are very advanced in minimisation of such risks especially when the personnel is trained on securely gathering and handling the data.

4. Conclusions and Outlook

Despite the unprecedented need for a complete understanding of complex bioprocesses to ensure product safety and efficacy, the bioprocessing industry falls short to utilise available digital solutions. The complex nature of the industry's products and production pipelines along with their tight regulation has led to the slow adoption of technological advancements. The manual-intensive steps render the industry prone to mistakes and process failures, while also preventing the full utilisation of available information. While these limitations and the benefits of automation and digitalisation are recognised by most, only a few examples of IIoT applications exist in the industry; many applications are only implemented in controlled conditions and remain yet to be challenged in the context of actual manufacturing operations.

The end goal of Industry 4.0 is the design of smart production facilities that are highly efficient and flexible by connecting machines through digital systems to enable real-time decision-making. The utility of IoT technologies are demonstrated by scientists at small scale as means of achieving this goal. Some companies also attempt to implement IoT elements into their operations, but most often these applications concern areas that are indirectly associated with manufacturing, such as supply chain or human resource management. Real-life IoT application examples available in the scientific, grey or white literature often lack details since the resource investment by companies to develop these solutions is substantial and leads to competitive advantage.

Each bioprocessing production is unique due to the different product and process specifications, which makes it nearly impossible to establish a universal IIoT framework for the industry. There have been attempts from Allotrope Foundation, Siemens, GE or IBM to standardise data or provide platforms to facilitate connectivity. However, companies interested in IIoT implementation would still need to develop their own solutions, which is very costly. Current regulatory constraints of the industry necessitate IIoT to be considered only during process development. The industry is concerned with potential need for product reapproval, breach of data, cyber-attacks or loss of IP protection due to extensive process changes induced by full-out IIoT applications.

However, the current issues around data integrity caused by user practices raises the question of whether this reluctance could also primarily stem from a lack of true understanding of how IoT operates. This highlights the necessity for training scientists and operators working in the industry to bring them up to speed with potential implications in the adoption and utilisation of the technology.

Although there are multiple benefits IIoT can bring to bioprocessing, they are not yet viewed sufficiently beneficial to justify the risks and investments associated with the implementation. Discussions with experts suggested that the industry first and foremost needs automation and digitalisation of its operations prior to any IIoT applications to be considered. This delay may be quite beneficial for scientists in bioprocess industries to gain the essential knowledge and training on digital advancements to allow them embrace IIoT more effectively. Updating of regulatory guidelines, development of the relevant standards and guidelines to accommodate the development and implementation of IIoT systems in bioprocessing are essential to reduce the associated costs and allow off-the-shelf solutions to be developed.

CRediT authorship contribution statement

DD conceived the study, LB designed and conducted the analysis and wrote the manuscript. DD provided critical revisions. DD and LB revised, formatted, and edited the text, and approved the final version of the manuscript.

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.

Data Availability

No data was used for the research described in the article.

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