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Conceptualizing data-driven closed loop production systems for lean manufacturing of complex biomedical devices—a cyber-physical system approach

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Abstract

A model is presented for shifting the manual intensive manufacturing process of complex biomedical devices towards more lean and efficient production process via application of concepts of cyber physical systems in combination with big data and analytics in a closed loop manner. The concept model is capable of handling high product volumes and variety, has ability for self-adaptation and correction in various operating conditions, and offers real-time quality control. The approach acknowledges the challenge of these industries operating in a strict regulated environment and the higher standards of built-in quality required by developing a closed loop process, proposed to be built in accordance to the requirements of regulatory bodies and current Industry 4.0 practices. The proposed model illustrates that modern manufacturing methodologies and concepts can be integrated and adopted in such highly regulated manufacturing environments and that the model can be deployed to different production scenarios.

Keywords: Cyber physical systems, Big data analytics, Industry 4.0

Introduction

Combinational medical devices are unique products from a manufacturing point of view as these are highly complex in nature and at times, are a high-volume product with multi size and part families. The need for multi-size and part families is to deal with differences in patient demographics in relation to gender, age, sex, patient anatomy etc. This poses a unique challenge for the organization as they need to scale to satisfy the high demand, but being a high-risk medical device, they must be very stringent with their manufacturing processes to be compliant with the regulatory needs. As a result, the degree of innovation and change in these regulated industries are comparatively lower than that of fast evolving industries such as automotive and consumer goods. Manufacturing process parameters are generally confined to a set design process setting window with no real-time monitoring. Usually end of line batch sampling techniques are used to audit the whole manufacturing process [1].

While these stringent checks ensure outgoing product quality, there is a tremendous yield loss and lack of efficiency in the manufacturing process, which adds additional cost to the price of these life saving devices. The motivation for this research is therefore fueled by the interest in applying latest manufacturing practices that will ensure high quality and greater efficiency for producing these complex combinational biomedical devices.

The logical solution to this, is adoption of more and more automation in the production process. However, adoption of automation in medical device manufacturing is easier said than done. There is no room for compromise on quality of goods produced. Food and Drug Administration (FDA) and other international bodies have established regulations and guidance for instances where automated process have been deployed within the manufacturing process. FDA as per its Code for Federal Regulations (CFR) Title 21 part 11–Electronic Records; Electronic Signatures–scope and application provides guidance on maintaining records and information in an electronic format [2]. It further states that for computerized systems, the agency intends to exercise enforcement discretion regarding specific requirements for validation of these systems. Title 21 CFR part 820–Quality System regulation Chapter I subchapter H–Medical Devices (21 CFR Part 820.70(i)) [3] specifically applies to automated processes and states that 'When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.' International Society for Pharmaceutical Engineering under a technical subcommittee Good Automated Manufacturing Practice (GAMP) is the golden standard for manufacturing and users of automated systems in regulated industries such as pharma or medical devices [4, 5].

The current trends of automation in the manufacturing industry are mostly driven by the fourth industrial revolution, also known as Industrie 4.0 or Industry 4.0. Initially introduced in Hannover fair in 2011 and officially announced as a strategic German initiative to lead the world in revolutionizing the manufacturing sector, Industry 4.0 represents the approach for the fourth industrial revolution with Information and Communication Technologies (ICT) laying the foundation for the revolution [6, 7]. Industry 4.0 is closely related to ICT, Internet of Things (IOT), Cyber-Physical Systems (CPS), Enterprise Architecture (EA), Enterprise Integration (EI), Big data, Smart factories and products, machine to machine communication and interfaces (M2M), cloud computing, augmented reality, virtual manufacturing, and intelligent robotics [8, 9, 10, 11]. Out of the many keywords that come up as synonyms to Industry 4.0, most common ones are CPS, IOT, Cloud, Big data, and M2M. Industry 4.0 defines a pathway to transform machine dominant manufacturing towards digital and smart manufacturing.

Against this background, this paper presents an approach of adopting and implementing such enabling technologies and automation within complex medical device manufacturing and aims to conceptualize a closed-loop production system that strives for making the current production system leaner and efficient.

Literature review

The major challenges posed by the fourth industrial revolution is a tenfold increase in consumer expectations. They are no longer impressed by one shoe fits all philosophy but rather demand for customization [12]. Healthcare industry is not indifferent to these customer centric sentiments and thus face a double-sided challenge of meeting the customer expectations and remain compliant to the regulations. This means that product lifecycles are thus a lot shorter, and the manufacturing processes therefore need to be upgraded quite frequently as opposed to traditional manufacturing. Traditional approaches to automation like that of dedicated manufacturing systems (DMSs) or flexible manufacturing systems (FMS) are not sustainable due to either being non-flexible to variety or if flexible, being too expensive and complex for relatively shorter product life cycles [13]. This led to the generation of idea of reconfigurable manufacturing systems (RMS). RMS consists of relative low-cost equipment or machine line that can be set up like that of a DMSs to manufacture a particular product but can be reconfigured in a short period of time to manufacture a different product. The integrated design of RMS facilitates flexibility in manufacturing operations through "modularity, integrability of resources, product and process customization, system convertibility, and diagnosability" [14]. It normally suits to manufacture sequential batches of different products which share common features in a RMS. Although RMS addresses the problem of flexibility and shorter life cycles, it falls short of addressing the issue of scalability as faced by the manufacturers. The logical upgrade to RMS is therefore automation, and where an RMS is automated, it is referred to as a reconfigurable manufacturing automation system (RMAS) [15]. Research has demonstrated that RMAS implementation in high volume manufacturing is quite a feasible option if the system is able to exploit the inherent flexibility of robots, vision systems etc.

Integrated systems—a cyber physical approach

With the increasing trend of smart manufacturing, advent of fourth industrial revolution and adoption of Industry 4.0 practices, rapid development of advanced manufacturing technologies and intelligent and integrated systems have taken place. While the adoption of RMS and RMAS tries to address the challenges of manufacturers in terms of product customization and scalability, it does not specifically address the demands for integrated and smart manufacturing. Thus, there are still inherent challenges present though for the implementation of these systems. A new paradigm of manufacturing automation is coming up lately which is highly focussed on core implementation of Industry 4.0 solutions called cyber physical systems (CPS). A CPS is defined as "an integration of computation with physical processes whose behaviour is defined by both computational and physical parts of the system" [16]. In comparison to regular embedded systems, CPS has been more promising in current times on connecting the physical to the cyber world [17]. Lee, Bagheri, and Kao [18] proposed a unified 5-level CPS architecture, namely the 5C architecture (Connection, Conversion, Cyber, Cognition, and Configuration) to be used as a guideline for implementing CPS in different industries. Bagheri et al. [19] added to this 5C architecture by suggesting an adaptive clustering method as an advanced analytical method for interconnected systems in CPS capable of identifying new working regimes in the 5C architecture autonomously. Muccini, Sharaf, and Weyns

[20] conducted a systematic literature review on self-adaption capabilities of CPS. Their review suggested that the primary concerns for adaption in CPS are performance, flexibility, and reliability across the different layers of CPS. Bangemann et al. [21] focussed on the evolution of classical automation systems into next generation industrial CPS and analysed widely used industry-proven integration technologies to do so.

An extension of CPS to manufacturing opens up enormous opportunities of achieving the goal of RMAS, Industry 4.0 and smart manufacturing. Development in computer science and information and communication technologies have meant a similar trend in the development of manufacturing systems, the resultant of which can be seen as the virtual world to be seemingly merging with the physical world. Often these systems when developed with focus on manufacturing, are termed as Cyber Physical Production Systems (CPPS) [22]. There are enormous expectations from CPS and CPPS such as robustness, autonomy, self-organization, maintenance, repair, predictability, efficiency, tracking, and tracing to name a few. Both CPS and CPPS can be deemed as the pioneer development responsible for fourth industrial revolution. The current scenario lacks the applicable framework needed for implementation of Industry 4.0. Mueller, Chen and Riedel [23] extended the reach of theoretical understanding of the Industry 4.0 and suggested that the development and usage of CPS prototypes and framework might help in realizing the sensor nets, coordination and interlinkages of the smart machines and usage of information and communication technologies for better scheduling of tasks and decision-making. Manufacturers and system designers though still are presented with a huge R&D challenge in order to come up with the solutions to the pre-eminent problems that would be needed to be solved prior to the realization of a true CPPS [24].

CPS in real world applications

While there is an abundance in literature on the CPS and the theoretical foundation of the system, numerous practical applications of the proposed theories solved real world issues. Ilić et al. [25] proposed a cyber-based physical energy system using data mining and novel sensing technologies for mathematically modelling the energy production and supply processes to meet consumer needs. In the power grid, Farzin, Fotuhi-Firuzabad and Moeini-Aghtaie [26] investigated the performance of smart distribution system comprising of micro-grids and proposed a novel hierarchal outage management system for improving the resilience of the system against unexpected disaster events.

Smirnov, Kashevnik, and Ponomarev [27] explored the idea of cyber physical social systems and proposed an information-based model for smart home devices that enables them to interact with each other in the cyber space while the physical devices interact in physical space. Lai et al. [28] analysed the issue around interoperability of various digital home appliances and proposed an Open Service Gateway Initiative (OSGi) architecture-based cyber physical home control system to allow users to control home appliances by an intuitive operation within the virtual environment. Liu, Sun and Liu [29] designed a control framework using full state information and nonlinear model predictive control to develop solutions for traffic control to be utilized in a Transportation CPS. Riaz and Niazi [30] suggested using human emotions and affective computing to understand the cognitive state of drivers in autonomous and semi-autonomous vehicles for improving the various aspects of communication in a vehicular CPS design. Wagh et al. [31] too

addressed an issue with the vehicular CPS (VCPS) where they defined a new architecture that enables High-level data fusion with human factor considerations within the VCPS.

CPS or specifically CPPS has also found a lot of application within the manufacturing industry. Uhlemann, Lehmann and Steinhilper [32] presented a concept for the realization of digital twin based CPPS for Industry 4.0. They argued that the biggest challenge in enabling of digital twin (DT) is data acquisition. As per them, data acquisition is possible through the existing systems that guarantee stable operation. The improvement in the system would be to acquire and combine all this data from these isolated systems into an overall system that would enable new possibilities in real-time production control applications. Tao et al. [33] drew correlation between DT and CPS and suggested that both CPS and DTs aim for achieving the goal of smart manufacturing by forming a closed loop of interaction and control between the cyber and the physical world. Lins, de Araujo, and Corazzim [34] deployed an in-process monitoring of tool wear of a computerized numerical control (CNC) machine based on CPS approach. They developed a machine vision system by combining software and hardware solutions capable of integrating different signals, network and physical components that were part of the monitoring system. Schreiber et al. [35] proposed something similar with a methodology to utilize the vast amount of data collected by the sensors in a CPPS to develop predictive maintenance and planning tools so as the maintenance cycles be defined objectively and be data-based. Wang, Zhang, and Zhong [36] addressed the issue of passive material handling in modern factories. They proposed a CPS enabled shop floor comprising of a proactive material handling system. They enabled all trolleys on the floor to be smart able to sense, act and interact with their surrounding and creating a digital twin model of the factory shop floor to reflect their real-time status. Tan et al. [37] proposed a 4-level closed loop cyber physical interaction architecture for industrial robot assembly process based on real-time data acquisition from the shop floor and fusion of the data for modelling, planning, and scheduling of the assembly process.

Cyber physical systems have started making a mark even in the healthcare industry. With the advancement in medical technology, more and more medical equipment and devices are now based on embedded and automated systems. Yeniaras et al. [38] proposed a novel CPS capable of performing robot-assisted magnetic resonance imaging (MRI)-guided minimally invasive heart surgery for aortic valve implantations. Jezewski et al. [39] designed a medical cyber physical system (MCPS) for telemonitoring of high-risk pregnant women through a network of body sensors connected to a central processing surveillance centre in a hospital. Lee et al. [40] discussed about the challenges in designing a robust closed-loop MCPS in a clinical setting for Patient Controlled Analgesia (PCA) and blood glucose monitoring and insulin administration for diabetic patients. Dey, Ashour, and Fong [41] too focussed on the challenges in designing of next-generation MCPS that would be secure, interoperable, scalable, and available. They insisted on the changing direction of healthcare towards being more CPS-based. Chai et al. [42] designed a prototype of hybrid brain computer interface for a biomedical CPS intended to combine cognitive neuroscience with that of physical systems to help people with disabilities. Silva et al. [43] proposed a model-based system for achieving early validation of MCPS with focus on reusability and productivity.

The synthesis of academic literature on CPS and CPPS, both in theory and in practice, suggests that the concept has been well developed and deployed in various scenarios. However, a knowledge gap is presented when it comes to deployment of CPPS in healthcare manufacturing and how that will fit within the regulatory framework that these industries operate within.

Data-driven smart manufacturing

The primary purpose of smart manufacturing is to improve the decision-making process in manufacturing. To be able to develop effective systems, it is key for the manufacturers to understand and pool in their knowledge to identify the problem areas and barriers to implement these smart systems [44]. O'Donovan et.al. [45] suggests the importance of modern smart manufacturing to be highly data-driven while the industry lacks the capabilities of industrial analytics. The challenge is to deploy these approaches being the diverse technologies and standards used across the industry and different factories. Efforts should be made to formalize the methodologies to deploy industrial analytics using technologies and standards that are aligned to the current resources and manufacturing environment. The manufacturing in future will be increasingly dependent on data leading to the digitization of manufacturing. This will in turn open the doors for data-driven manufacturing modelling approaches and that virtual, augmented-reality and predictive modelling will become the routine constructs of manufacturing replacing the traditional mathematical-modelling approach. The generation of this data and the modelling based of this data will lead to monitoring and prediction of the production process, equipment health status and that fault prediction will also become a new norm within manufacturing [46, 47].

The maximization of the integration of big data analytics (BDA) is key to build a comprehensive CPS architecture for making faster and better decisions in monitoring and control of these complex systems. Data analytics facilitate a crucial role in enabling Industry 4.0 and the collaborative data analytics framework is suggested to positively affect the cyber-physical production systems in terms of cost reduction, operational efficiency, product quality improvement, and improved customer experience. The collaborative analytics also benefits manufacturing and operational planning process by shortening production lead time, lowering product cost, quicker time-to-volume ratios, and fine-tuning of the manufacturing operations and capabilities [48]. Deploying data-driven CPS in medical device manufacturing has many promising applications. Of the many important uses, the industry will hugely benefit from this approach for manufacturing process monitoring and quality control. It is a regulatory and compliance requirement as well, per good automated manufacturing practice (GAMP), FDA 21CFR820/210/211 and 21CFR11 on electronic signatures and records.

The first and foremost requirement for data-driven manufacturing is data collection from the physical layer of the CPS. IOT and Cloud computing (CC) provides new methods for intelligent perception and connection of anything and enables demand based efficient use of resources, which enables the modern manufacturing to overcome its key bottlenecks in their journey of transformation from production-based manufacturing to service-based manufacturing. Tao et al. [49] proposed the classification of manufacturing resources and services and the inter-relationship between these two. They suggested

a five-layered approach for realizing the intelligent perception and access of manufacturing resources based on IOT technologies. These layers are that of resource layer, perception layer, network layer, service layer, and application layer (Fig. 1). While preliminary research is presented in resource perception and access in cloud manufacturing (CMfg), it is recommended that many efforts are needed first in design and deployment of the perception devices (e.g., optical sensors). Cloud computing and Internet of things (CCIoT)-based CMfg brings together these key technologies to work in conjunction to bring the concept of CMfg to reality [50]. Based on the historical process data and the current data being collected of the factory sensors, certain conditions can be easily related to quality control of the products. Synthesizing these factors related to time and causality, a predictive model can be developed using relevant data algorithms to predict production/system abnormalities [51].

For the system to be able to make smart decisions, it is important that the system can interpret the data in a meaningful way and basically be capable of converting the raw data received in the communication layer and converting the data to smart meaningful data before being passed onto the cyber layer. Data collection, data pre-processing, data storage, data mining, and data visualization are therefore to be effectively compiled together for a BDA model to be generated for further high-level CPS applications [17, 52] highlighted the challenges faced by manufacturing entities with big data analytics and proposed a CPPS that uses data analytics to enable production visibility. Data analytics is argued to be still an issue with the CPS though, as an effective analytics system for CPS integration is yet to be realized. The elements of data analytics which are data collection, data analysis model generation, model execution, and data visualization are applied separately and there is no system for the elements to work in tandem.

Role of big data analytics in CPS

Virginia Rometty, IBM's ex-CEO, recently updated the analogy of 'Data is the new oil' to 'Big data is the new oil' [53]. The most common annotation for big data was first conceptualized by [54] where big data was characterized using the 3 V model: volume, velocity, and variety. This model was further refined and extended by [55] to a 5 V model: volume,

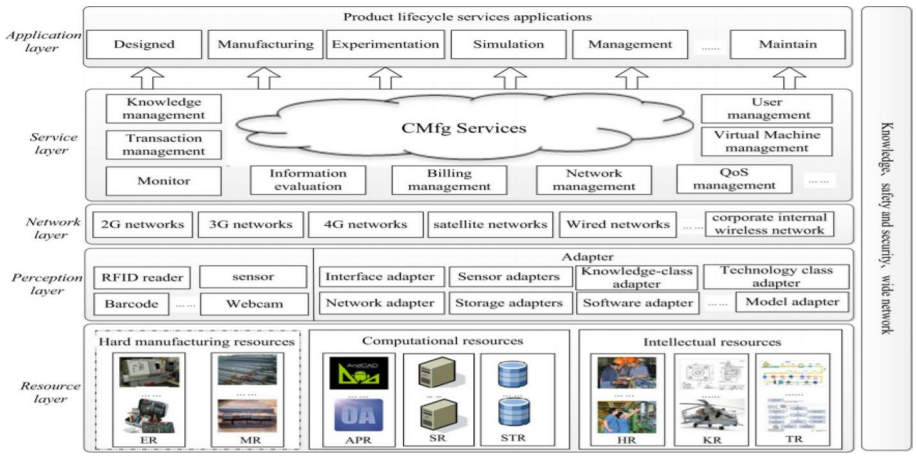

Fig. 1 Architecture of intelligent perception and access of CMfg resources based on IOT [49]

veracity, velocity, value, and variety (Fig. 2) and focuses mainly on three main techniques, namely, clustering, classification, and prediction [56]. Despite of this enormous data generation in the enterprises and a lot of tools available for analysing this data, a lot of the organizations are struggling or underutilizing these resources due to the tool's complexities and lack of technical expertise [57]. For the success to be achieved from big data, a top-down management approach is needed focussing on solving the entire problem around IT infrastructure and technical expertise needed as the implications of big data in manufacturing are huge and it's too big of a risk and cost to be left behind in the digital age [58].

A big part of designing a robust CPS is designing the system with a closed-loop feedback control. For the system to be adaptive and responsive to the complex and continuously changing dynamics in the surroundings that they operate, they rely heavily on the data being collected and processed for smart decision-making and overall control. For the CPS to be responsive in real-time, it can no longer rely on humans and specifically software engineers to alter or modify its run code to adapt quickly. CPS and other systems such as Digital twin etc. aim for achieving the goal of smart manufacturing by forming a closed loop of interaction and control between the cyber and the physical world. It does so by virtue of its virtual models and its ability to simulate the physical world and its evolution [33]. Otto et al. [59] addressed the issue of real-time response by proposing a novice approach for automation system engineering. This approach otherwise termed as 'synthesis approach' by the authors requires the sematic knowledge base and product model of the desired system outcomes that will in turn produce a hybrid timed automation of the system, which can then be transformed into software code automatically. This

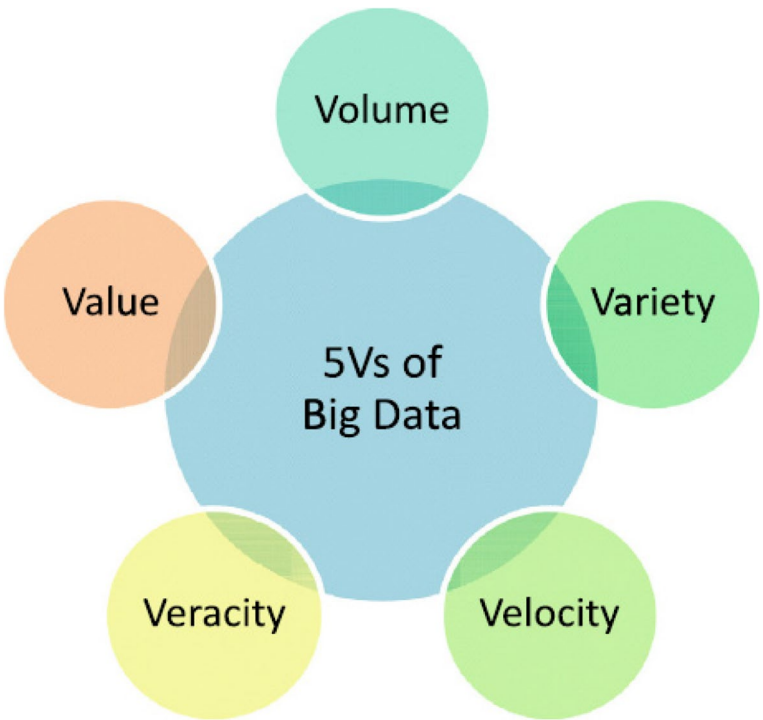

Fig. 2 5 V's of big data [55]

approach no longer requires the software code to be manually coded or software block libraries to be created for compositional approach of system engineering. Leitão et al. [60], Leitão and Restivo [61] proposed an adaptive holonic control architecture, which they termed as 'ADACOR' for distributed manufacturing systems. It is an adaptive control architecture that allows the control system to be as centralized (Stationary State) as needed and as decentralized (Transient state) as possible. This meant the system would be centralized in decision making when it comes to optimization and then would be decentralized to response to the disturbances and unexpected events. Iqbal et al. [62] proposed a novel CPS modelling approach named hierarchical spatial–temporal state machine (HSTSM) combining the soft-computation techniques to deal with large volumes of data characterized by spatial–temporal correlations.

All these approaches and decision-making models, however, fundamentally rely on data being collected and processed, either from factory shop floor for manufacturing or smart systems deployed in various other applications, such as MCPS in healthcare, smart devices in home, IOT sensor framework in energy grids. Atat et al. [63] among the many aspects of their detailed overview of the big data enabled CPS, covered the importance of data mining and data cleansing for it to be ready for real-time data analytics. Miloslavskaya and Tolstoy [64] elaborated on the emerging concepts of big data lakes and fast data: one which handles the huge influx of raw data in its native format and the latter being time-sensitive requiring systems with low latency and high processing speeds, key for real-time analytics. Zhou et al. [65] studied a big data-driven energy management system in smart grids and discussed the challenges in the industrial development of such systems in relation to the IT infrastructure needed to support it, data collection, integration, sharing, processing, analyzing, and governance. Koseleva and Ropaite [66] on the other hand investigated the application of big data in a smaller context in applying the analogy into sustainable buildings by using BDA for energy consumption in buildings. They too pointed out the main problems with big data and the traditional databases which are more friendly for getting the data stored rather than the data being analysed. With traditional databases, it's only possible to get a small subset of data out and analyse it but very difficult to see the whole data and derive patterns or learnings out of it.

Like most of the obvious applications that big data have found in industrial setting, healthcare is one of them too. With the healthcare data ever growing with time, the sector is undergoing significant changes in response to globalization, mobility, and social networking [67]. Wan and Gurupur [68] define healthcare data analytics as "a study of methods and techniques to analyze data, discover new information and knowledge, link data in terms of its semantics, and describe data to other informaticians, managers, and other stakeholders" and calls out the stark difference between healthcare informatics and healthcare data analytics. Wills [69] suggested the use of all three forms of data analytics small data, predictive modelling and real-time analytics for adoption in the healthcare systems to improve the quality of care and being cost efficient at the same time. Thanks to BDA, healthcare is moving away from an ideology of uniform treatment to personalized care. Since the emergence and adoption of electronic medical records, a new trend in healthcare industry known as 'Treatment Pattern Mining' is developing which is using BDA and its capabilities to offer customized and patient specific treatments, rather than a one shoe fits all approach of traditional medical practice

[70]. Chen and Islam [71] studied the application of big data in medical image analytics, medical signal analytics and in genomics. Zhang et al. [72] proposed a healthcare CPS supported by cloud and big data for patient-centric healthcare application and services. Zhang and Zhang [73] discussed the influence of big data on clinical research in context to traditional Chinese medicine practice where the focus is shifting from 'causality interference' to 'correlativity analysis.'

It is therefore evident that big data is playing an important role in modern manufacturing in general and healthcare industry in specific. It has been responsible for a paradigm shift, just like that of CPS where the trend is shifting from universal to customization. Although there has been significant research into the impact of big data analytics, little has come into light when viewed in context of application to building a robust CPS and specifically CPPS. There have been pointers that tells us that the possibilities are huge from the amalgamation of CPS and BDA, but more efforts are needed to bring the abstract to practice and understand and confront the challenges in doing so.

Knowledge gaps

Summarizing the findings and observations from the literature review as below:

- With the adoption of Industry 4.0 practices and associated ICT systems, there is a significant shift from universal one-shoe-fits-all approach towards customer-specific customization. This is true especially for the healthcare industry including manufacturing of complex biomedical devices.
- RMS and RMAS can address current issues around flexibility and scale but fall short of addressing the needs of integrated and smart manufacturing that are self-adaptable to ever changing surrounding environmental uncertainties.
- CPS and CPPS combines the concepts of RMS or RMAS and Industry 4.0 smart factory needs, but there are inherent challenges faced by organizations in designing and conceptualizing these complex systems which needs to be addressed first. These challenges relate to IT infrastructure needed to support these systems, technical expertise etc. An important challenge to address is the strong need for standardization in the way that different cyber-systems interact with each other and cluster of information that is data-ready for process improvement and optimization.
- For CPS and CPPS to be dependable and adaptive, they need to be able to learn and adapt as per the changing surroundings in real-time. This brings in the importance of CPS to be data-driven and the need for maximisation of BDA to build a comprehensive CPS capable in responding in real-time.
- CPS has a lot of real-world applications and has been adopted in a lot of industries such as energy, transportation, manufacturing, and healthcare. Within healthcare, which is the focus of this research, most of the literature caters to the application of CPS in a clinical perspective like that of MCPS, and very limited or no evidence has been found on the use of CPS within healthcare manufacturing and regulated industries.
- BDA is argued to be key in developing CPS to be responsive in real-time and in developing decision-making models for CPS within various industries, including healthcare. Again, all the application within healthcare were found to be within

clinical practice and less or no evidence was found for the use of BDA enabled CPS within complex biomedical device manufacturing.

From the above, it is evident that there exists a potential wide gap in the literature when it comes to application and adoption of CPS and BDA to manufacturing of these complex combinational biomedical devices. Both these concepts have only been studied from a clinical practice point of view and as such, the need for exploration of these into regulated manufacturing is prominent.

Methods

The development and implementation of a CPPS will require addressing the following essential issues: (1) flexibility at scale—the need to develop a solution that would enable to manufacture these highly specialized product families in small batches at scale, (2) self-adaptive closed-loop control—the need to develop a solution that would enable the manufacturing process to respond to changing variations and uncertainties without any human intervention, (3) real-time quality control—the need to develop a solution that would enable real-time monitoring and quality control of the manufacturing process rather than to rely on batch sampling process to audit the whole manufacturing process. To deal with these challenges, research is conducted on two fronts—exploring theoretical models that exist in literature to guide on the approach to be taken for developing such CPPS and looking into other non-regulated manufacturing industries to see what solutions already exist for the presented issues and exploring how they can be retrospectively deployed in a regulated manufacturing environment.

A model for implementing CPPS is presented by [74] where the structure and flow of assessment for analysis and development of CPPS can be directly adapted to develop a model for most of the production scenarios (Fig. 3). With a human-centered approach, the model provides a baseline for any undertaking of a CPPS deployment.

The model can be reimagined when developing such CPPS from scratch. The above model assumes that the needed infrastructure for deploying such capabilities is already

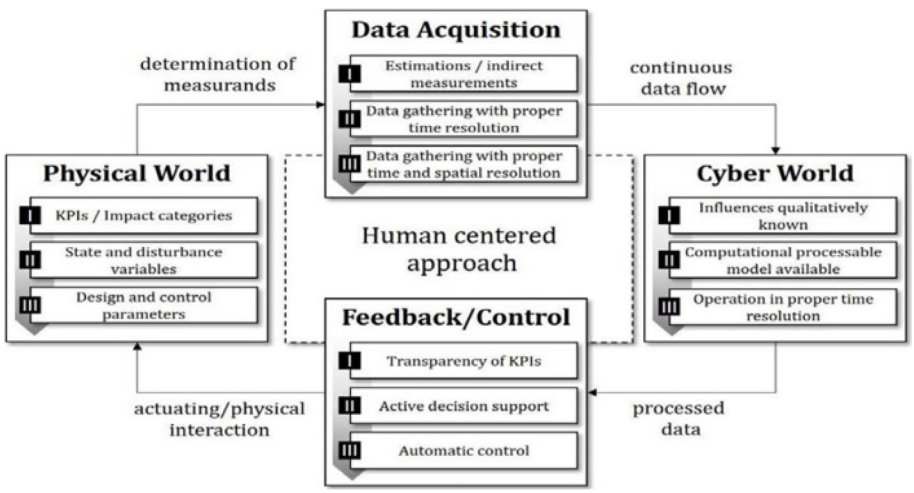

Fig. 3 Development of CPPS in learning factories [74]

existing, which, however, may not always be the case. The medical device industry particularly has for so long adhered to manual processes, that deploying such systems will need new systems to be designed from scratch. A more practical version of the model is proposed in Fig. 4, where the model accounts for the whole process design lifecycle which is based on the idea of Action Design Research (ADR) for artefact generation through continuous improvement loops as proposed initially by Sein et al. [75] and further improved by Mullarkey and Hevner [76].

The method for this research, therefore, is a mixed method approach where existing theoretical models in the literature on CPPS and broadly over Industry 4.0 have been bootstrapped with existing real-world solutions in practice in non-regulated industries. The aim is to come up with a solution that would suffice the research needs as highlighted in the previous section and a solution that would be acceptable for both the business stakeholders and regulatory bodies. The following sections will take a deep dive into coming up with the experimental set up needed for this study.

Machine design

To develop a CPPS model, the system and hardware design engineers undertake a design activity for a specific case study. The objective of this activity is to incorporate the necessary enablers for CPPS deployment. As mentioned earlier, the medical device industry has minimal automation, so the initial project deliverable is to create automation solutions that integrate IoT sensors, advanced vision technologies, and other components required to accomplish CPPS goals. While the detailed design process is beyond

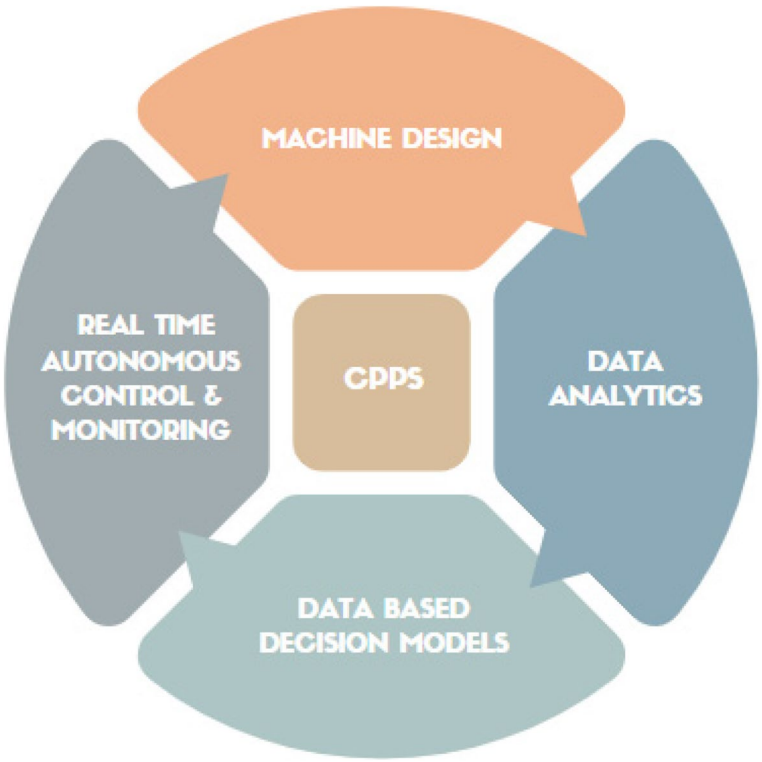

Fig. 4 Proposed approach for model development of closed-loop autonomous CPPS

the scope of this paper, subsequent sections will provide a brief overview of the system design architecture and physical machine design for a particular case study.

Data analytics

Once the infrastructure needed to build a CPPS is commissioned, a custom off the shelf solution is engaged to help with the automated data collection and analysis. For this project, InfinityQS® application is used to collect the data generated by the system.

Figure 5 shows the system roadmap for data collection. The application uses a DMS, which is an interim repository for data gathered from external sources, in this case, the control PC on the system. Using a DCS interface, this data is passed onto SPC client's data entry process. The DCS interface imports the critical data such as process state, specification limit, subgroup information into the central servers, thus, eliminating the need for manual data collection and entry. The data is collected in two streams, one validated that becomes part of the overall QMS and remains untouched by any process. The second unvalidated stream which is a carbon copy of the original data, is used for engineering and reporting purposes. The outcome from analysis of this data feeds as an input to the data-based decision models.

Data-based decision models

In regulated industries like medical device manufacturing, process characterization is a common approach used to ensure that the manufacturing process operates within a safe

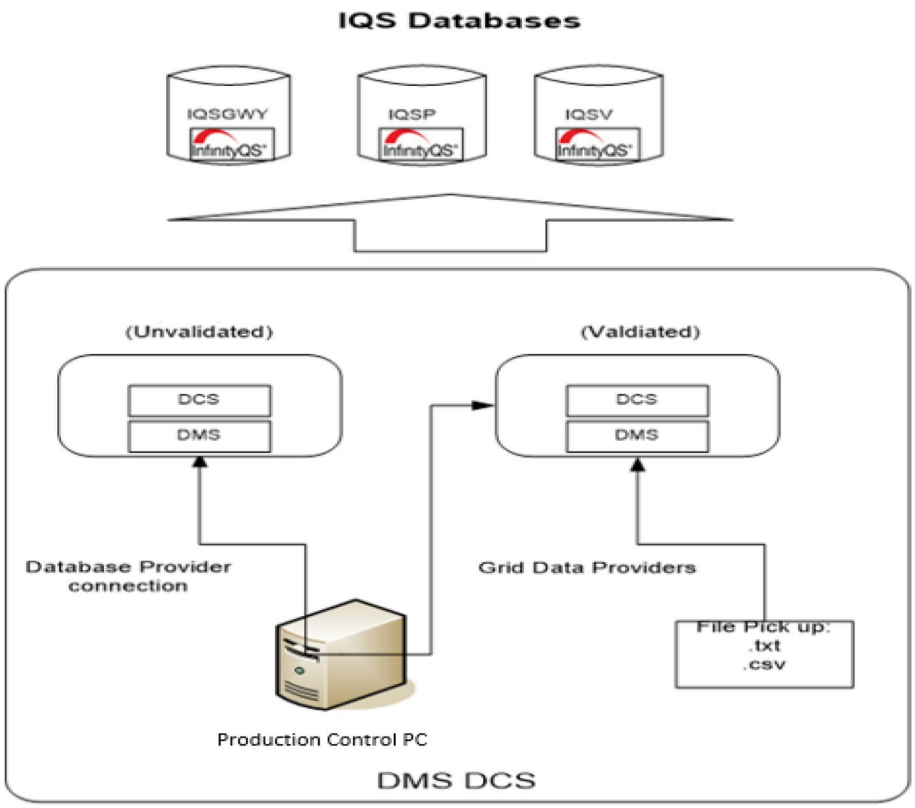

Fig. 5 Data collection by the SPC software

and compliant zone. This is typically achieved through design of experiments (DOE), a statistical technique that helps establish a regression relationship between the inputs and outputs of a process. For the given output characteristics of a product, DOE helps identify the critical process parameters (CPPs) that significantly impact the process outcomes, and those that do not. These CPPs are then closely monitored and controlled throughout the manufacturing process to ensure product quality and consistency.

The regression equation developed from these DOEs for CPPs serves as the foundation for the algorithm used in data-based decision models. The concept is that when the system detects the process going out of control, it can automatically adjust the corresponding input CPP, depending on the characteristic, to bring the process back into the desired range.

Real-time autonomous control and monitoring

With the implementation of CPPS enablers and real-time data analysis, the system becomes self-sufficient to achieve autonomous control. Depending on the required level of monitoring, the system can detect and correct out-of-control situations using data-driven decision models and keep stakeholders informed of the process state. The InfinityQS® SPC application used as part of this project has built-in features to relay live process information to the production floor staff and issue alerts when the system is unable to bring the process back in control due to unforeseen circumstances.

Conceptual model development—a case study

Most of the elements of the above proposed model are generic and achievable and readily deployed in several industrial settings. Customization is needed specifically when it comes to machine design and developing quantitative data-based decision models as they are highly application and process nature dependent. A case study is undertaken which involved an Ireland-based, independent coronary cardiovascular stent catheter manufacturing business. The objective is to do value stream mapping of the current catheter manufacturing process and proposing a closed-loop CPPS model to replace the current manufacturing process to resolve the three issues highlighted in previous section. The current manufacturing process of the stent catheters is highly manual in nature involving product builders or operators working on a line, taking the components through various processing steps like assembly, polymeric bonding through concentrated heat application, and inspections (Fig. 6).

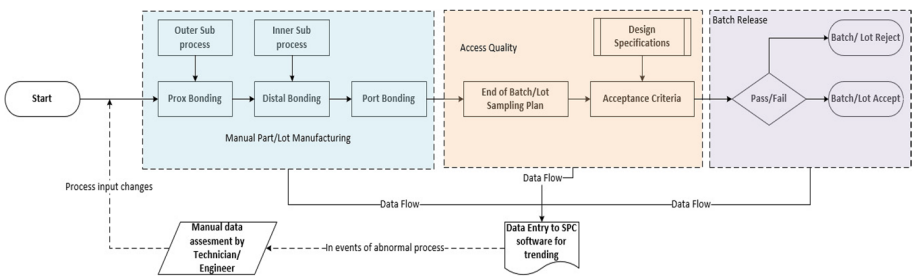

Fig. 6 Process mapping of current manufacturing process

Flexibility at scale

The first issue for the manufacturer is that catheters like most consumable medical devices are high volume high complexity multiple product family items. The pinch point currently lies within time consuming changeovers between different sizes and different product families and associated paperwork involved with changeovers to maintain full traceability, as driven by the regulatory framework. Pharmaceutical and life sciences industry somehow face the same challenges and as a result, have adopted the International Society of Automation's (ISA) standard for batch control systems. ANSI/ISA-88.01–1995 and ANSI/ISA-88.00.02–2001 standards on batch control provides golden industry standards for batch control through recipe management and batch execution software which have substantially proved their reliability and capability due to implementation in these industries [77, 78, 79, 80].

The design within the S88 model starts with the process model which is essentially the knowledge of the process to be realized. This knowledge model is then stepwise built up from general recipe to control recipe. The resultant control recipe is the final iteration of the sequence of steps to be taken to get desired process outputs. The physical control model in turn comprising of the equipment and physical control, deals with sensor and actuators controls which when combined with the control recipe generates the overall procedural control essential for attaining end goal of batch control (Fig. 7). It is therefore eminent that solution for this issue exists separately, as in, available robust system model architecture from the ISA standards that are needed to be combined with a proposed automated machine/cell design. The resultant solution would suffice the needs for high volume catheter manufacturing and the regulatory requirements of FDA and other compliance bodies.

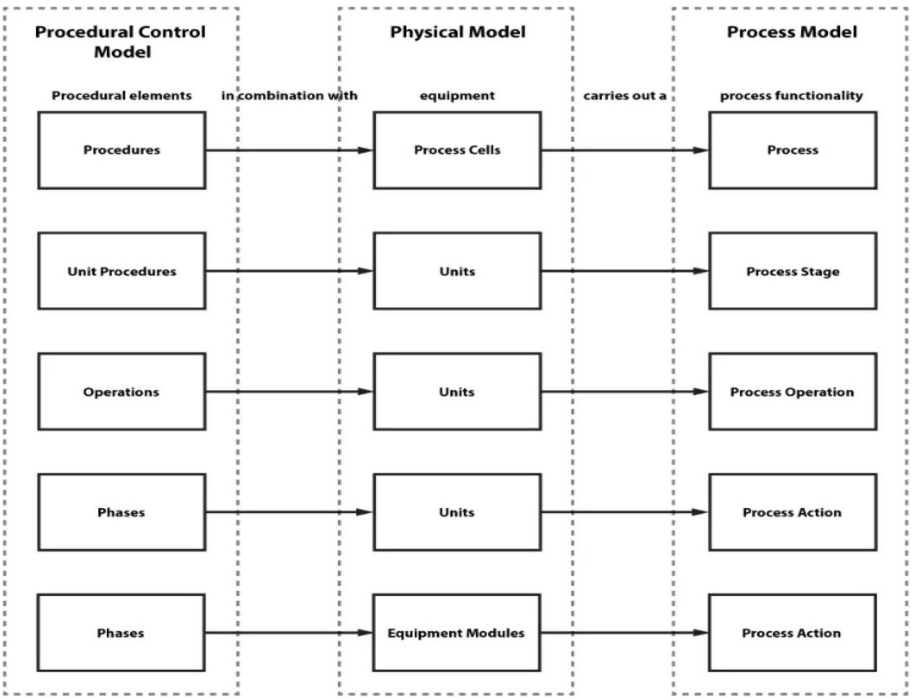

Fig. 7 Process Control and Equipment view of ISA 88 [77]

Self-adaptive closed-loop control

The next issue is around self -adaptable capability of the system to respond to changing physical conditions of the process (material variation, change of surroundings etc.), the extent of literature and industry standards were explored to see what solutions or concepts are already in existence or being investigated for feasibility. This problem theme is essentially the demand of the research question for the developed solution/system to be 'smart' and have inherent capability for adaptive control. Leitão et.al [60], Leitão and Restivo [61] have worked extensively on this and proposed an architecture named 'ADACOR'. ADACOR or adaptive holonic control architecture for distributed manufacturing systems is proposed as an adaptive control architecture that allows the control system to be as centralized (stationary state) as needed and as decentralized (transient state) as possible. The proposed adaptive production control shares the control between supervisor and operational holons and splits the control evolution into these two alternative states: stationary state, where the system control uses coordination levels and the supervisor role to get global optimisation of the production process, and the transient state, triggered with the occurrence of disturbances and presenting a behaviour quite like the heterarchical approach in terms of agility and adaptability. This implies the system would be centralized in decision-making when it comes to optimization and then would be decentralized to response to the disturbances and unexpected events.

Apart from the conceptual model architecture(s) such as ADACOR (Fig. 8) and other models presented widely among the literature, there are numerous industrial standards and architectures in existence or currently under active development. The European Committee for Standardization (CEN) has published standards for advanced automation technologies and their applications under CEN/TC 310 [81]. Similarly, International Standards Organization (ISO) has published numerous standards and continuing to develop further standardized approach to smart manufacturing. ISO/TC 184 standards for Automation Systems and Integration has multiple sub committees all aiming to develop a reference model for smart manufacturing [82]. International Electrotechnical

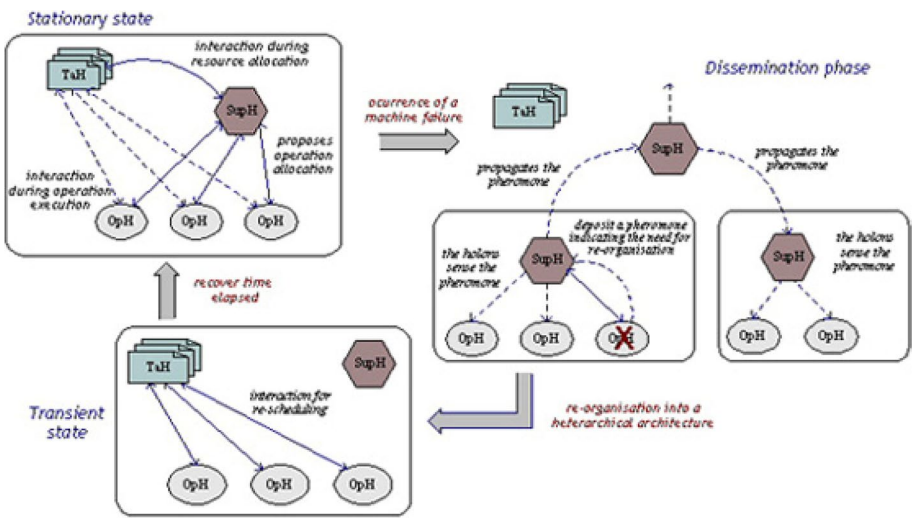

Fig. 8 ADACOR architecture

Commission (IEC) has workstream TC65 for development of international standards for systems and elements for industrial process measurement, control, and automation [83]. In fact, it has been found that there are gaps and duplication within the standardization activity for smart manufacturing among international standards that ISO and IEC have formed a joint working group for developing an international reference model for smart manufacturing [84]. ISO/TC 184 and IEC TC65 formed ISO-IEC JWG21 in 2017 with a goal of coming up with a single reference model to align the requirements of various manufacturing system users and consumers.

The group is working on a technical report IEC TR 63,319 Smart Manufacturing Reference Model (SMRM) that has reviewed the various SMRMs across different countries and proposes a meta-model based on that (Fig. 9) [85]. Among the many SMRMs compared were Intelligent Manufacturing System Architecture (IMSA, China), Reference Model for Smart Manufacturing Standards (France), Reference Architecture Model for Industrie 4.0 (RAMI4.0, Germany), Industrial Value Chain Reference Architecture (IVRA, Japan), Smart Manufacturing Ecosystems (NIST, USA), Scandinavian Smart Industry Framework (SSIF, Sweden) etc.

The JWG21 TR and various other reviews [84, 86, 87] have highlighted the fact that among the many model architectures reviewed, no single model will suit all problems with abundance of overlap and conflicting terminologies across different models. JWG21 is, therefore, now developing a Unified Reference Model for Smart Manufacturing (URMSM) with an aim to provide common terminology that will facilitate comparison and thereby enabling to be able to select the best model for intended use and purpose [88]. Developing SMRM is solving one part of the issue, which is developing the intelligent system. The other part of the issue is for the system to be adaptive. ISO 14649 and ISO 10303–238 (known as Step-NC) aimed to replace the traditional ISO 6983, all under the umbrella of ISO TC184/ SC1 for Industrial Cyber and Physical Device control [89], focuses on achieving Step-NC compliant manufacturing in loop of CAD/CAM/CNC. Step-NC aims to describe tasks as 'what-to-do information' rather than 'how-to-do information', however, the industry still awaits a truly intelligent and adaptive controller. These standards for smart manufacturing have so far provided a solid foundation for

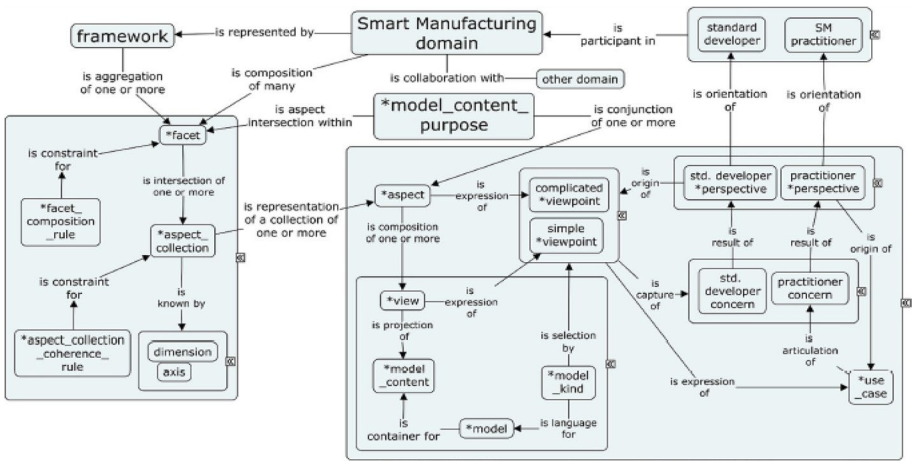

Fig. 9 ISO-IEC JWG21 meta model [85]

developing smart manufacturing automation. However, combined with advanced algorithms, connectivity, and computational power, much work needs to be done for being able to develop a self-adaptable system, capable of responding to dynamic alterations in the manufacturing environment [87].

Real-time quality control

Combinational biomedical devices such as those of stent catheters have been classified as class III medical devices which is the highest patient risk category for a device, the manufacturing and quality control of these devices have not been able to keep a pace with the advancement of the device design technology. As a result, the manufacturers have till date clung to the almost a century-old end of line, acceptable sampling methods, partly due to either destructive nature of the tests and mainly business conservatism and hesitancy in adopting new technologies [1]. ISO 13485, the international standard for medical devices and its quality management systems, has laid down multiple requirements for regulatory purposes for the manufacturing of medical devices. The organizations are required as per regulation to conduct validation of the manufacturing process to be able to evidently demonstrate the ability of the process to achieve consistent results. The organizations are also required to monitor and measure both their processes to ensure compliance to the pre-defined process outputs and their products to verify that the manufactured product has met the product requirements [90]. For achieving the desired product quality, FDA suggests the manufacturers to have extensive understanding of their processes and critical product and process parameters along with the ability to control processes through quality systems and strive for continuous improvement [91]. It continues to emphasize the need for industries to move away from classical batch release and control strategies towards real-time release testing (RTRT) through utilization of process analytical technologies and tools (PAT). The aim is to be able to generate real-time information on various nuances such as process parameters, input and in-process materials, and final product attributes. Within the PAT framework, the tools are categorized either as Multivariate tools for design, data acquisition and analysis, process analyzers: at-line, on-line, or in-line, process control tools or continuous improvement and knowledge management tools [92]. The PAT framework provides guidance to overcome the challenges of classical quality control; however, some challenges still prevail. Complex statistical process assessment is not something easily understood by the non-technical shop floor staff. The use of statistical infographics to visualize the real-time data is helpful but the interpretation of that data to make efficient decision making for making process changes is still a challenge. Moore [1] focuses on addressing some part of this challenge by pointing out the need for industry currently using classical quality control approaches to move towards more modern quality control methodologies integrated with real-time assessment technology grouped in a simple format that is readily understandable and usable by non-technical shop floor staff.

Conceptualizing CPPS model

Based on above findings, an effort has been made to conceptualize a CPPS model for the given production process.

The concept closed-loop model (Fig. 10) attempts to combine the elements of the theoretical CPPS model as proposed by [74] along with the findings on solutions for the three main issues. The model needs to be realized in accordance with the qualification framework of the regulatory bodies that would prove out system capability in terms of robustness, repeatability, reproducibility, reliability, traceability, quality through real-time statistical process control (SPC) and from the business interest point of view in terms of achieving autonomous capability, better overall equipment efficiency (OEE), reduction in cost of goods, scrap etc.

The conceptual model forms the backbone of the system/software design architecture of the proposed CPPS to be deployed for autonomous catheter manufacturing (Fig. 11). The architecture design arranges the software entities for the application installed on the control PC. The right side of the design shows the reusable objects—assembled as dynamic link library (.dll) files. The upper middle shows any reusable objects. The design also arranges the derived control classes for interactive programming application. The squid classes act as mediators between objects, allow abstracted, procedural component-code to be stable and allow isolation for the interactive objects.

The machine class acts as container for objects under the machine level, initializes those objects and provides the sequence processing for the interactions of those objects. The station class acts as the container for the station level. The user-interfaces are derived and developed objects for the interactive programming application. User-Interface objects appear on the left side of the figure. Lastly, an XML sequence file provides the explicitly predetermined series of tasks software objects perform. In performing the tasks, the objects control the hardware and interface with the user and databases. The Squid classes perform the explicitly determined data acquisitions and decision-paths required to support the XML sequence.

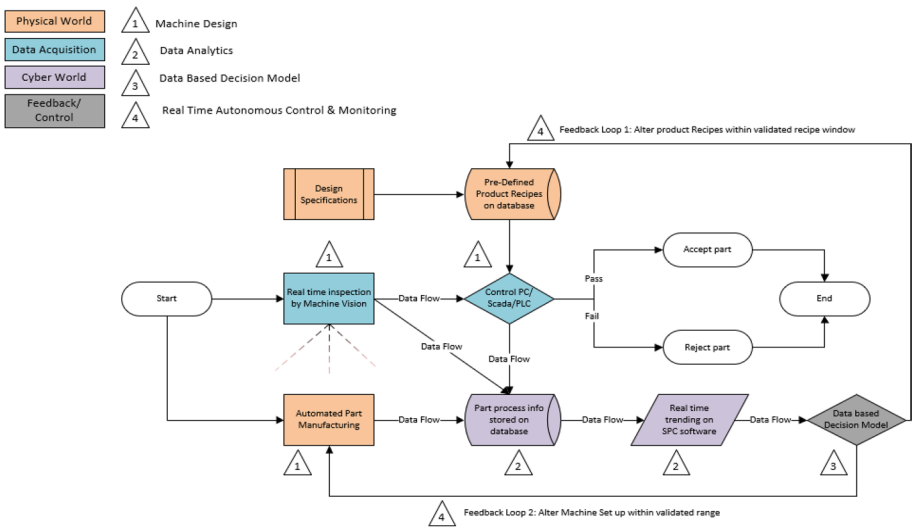

Fig. 10 Conceptual closed-loop reconfigurable CPPS

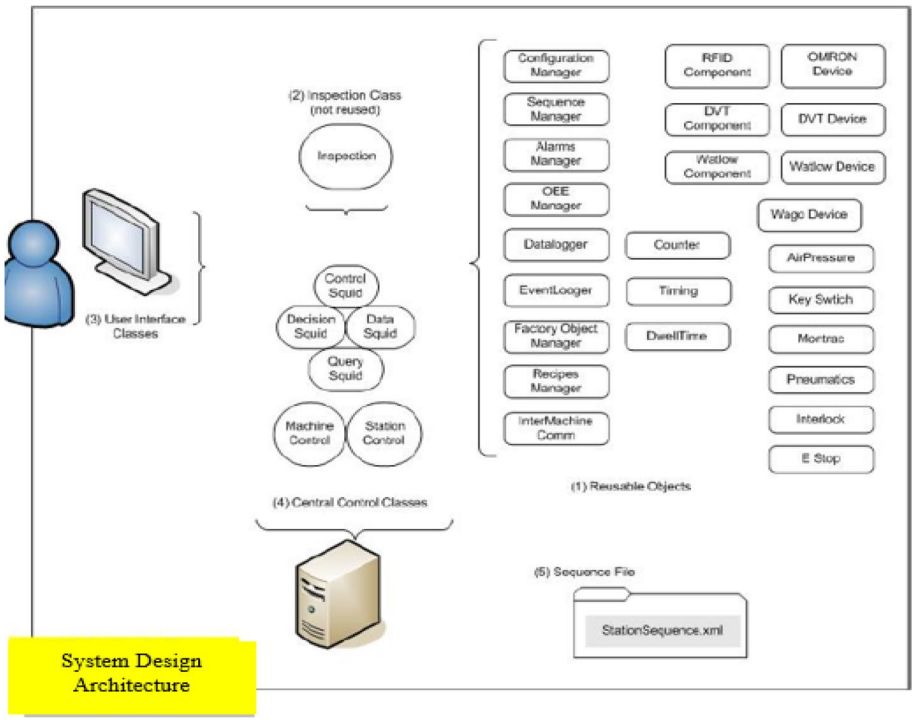

Fig. 11 System/software design architecture for the CPPS

Concept CPPS model vs SMRM architecture: research novelty

Ahmadi et al. [93] attempted to answer a few key questions as part of their research, couple of which are very relevant to the context of this research as well. They presented a comparative analysis of key architectures for Industry 4.0 and suggested standards from the pool of standard bodies relevant and applicable for Industry 4.0. They linked SMRM's four component layers and interfaces with the specific standards. This model of smart manufacturing ecosystem architecture and standards was utilized to compare the conceptualized closed-loop CPPS. It is key to understand the novelty of this research effort, since adaptation of SMRM into developing 'production' solutions is not novel and has been attempted before. Park and Febriani [94], for instance, proposed using certain characteristics of Industry 4.0 based on RAMI 4.0 SMRM architecture to transform a robot welding system to a smart welding system. Head-to-head comparison of developed models/systems with the theoretical SMRMs, however, is scarce in literature. It's important therefore to analyze the stack up of the model against the standard SMRMs. Figure 12 details the stack up of the proposed model's system design architecture with the hierarchical architecture and SMRM's four component layers and interfaces with the specific standards.

The inter-layer communication protocol set out by Open Platform Communication-Unified Architecture (OPC UA) IEC 62,541 standard allows the flow of information and data in real time in a safe manner that forms the backbone of this control loop. Closed-loop feedback control so far was limited to device level for stabilizing a process, which is now being attempted to be extended beyond the device level to the integrated system

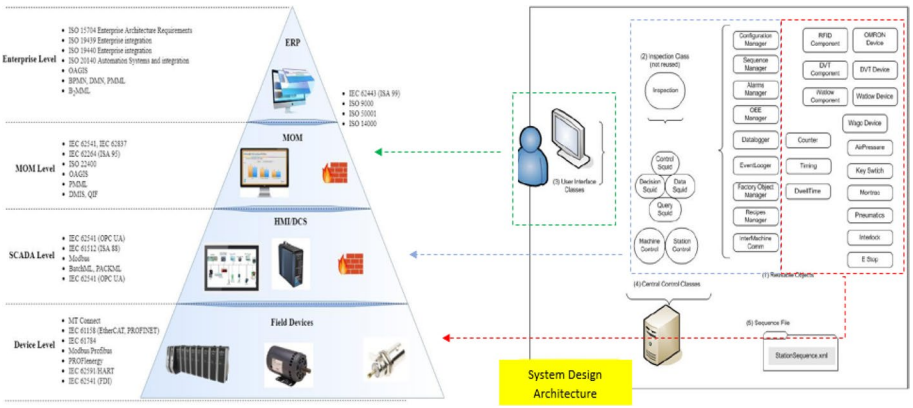

Fig. 12 SMRM architecture vs proposed CPPS system design architecture

level. The desired outcome is achieving a higher level of control not just at the process level but at and up to the enterprise level.

Results and discussion—model implementation

A test rig is built based on the idea of conceptual CPPS model and the system design architecture. Machine design and build phase provides the enablers to automate the three key laser bonding steps for catheter manufacturing process as shown in Fig. 6. A state-of-the-art vision system is built into and validated for use into the rig (see Fig. 13a–c). This enables the system to capture real-time processing data for the laser bonding process.

A dynamic recipe management system based on ISA 88 standards is created and deployed on the database the rig is connected to. This allows the rig to attain flexibility at scale as product builders are no longer required to go through a changeover checklist to switch between different product families. As soon as a part number is scanned in for production, the system automatically downloads the pre-loaded recipe from the database to run the machine. The recipes are dynamic in nature as the system is designed to influence some CPPs within a validated production range. A restriction is embedded in the recipe management module of the system design for feedback loop 1 as per Fig. 14. Every product family and manufacturing process validated previously had either a set point or a validated processing window associated to it. Majority of the out of process conditions when caused, are primarily managed by either moving the process parameters within the validated window or altering the machine set up within the validated range in the manual process. In the automated process, the data models will do the same. However, the system is designed as such that if the model feedbacks any value outside the pre-determined validated range, the feedback input is rejected by the system. Figure 14 shows how the system handles a typical out-of-control process. Once the system is triggered, data squid analyses the data and passes it on to the decision squid. The decision squid then based on the data-based decision model feedbacks either to alter recipe or alter machine set up. However, that value is only accepted if the parameter in question is set to 'true' for offsetable parameters and the value lies within the failure lower and upper specification limit (LSL/USL).

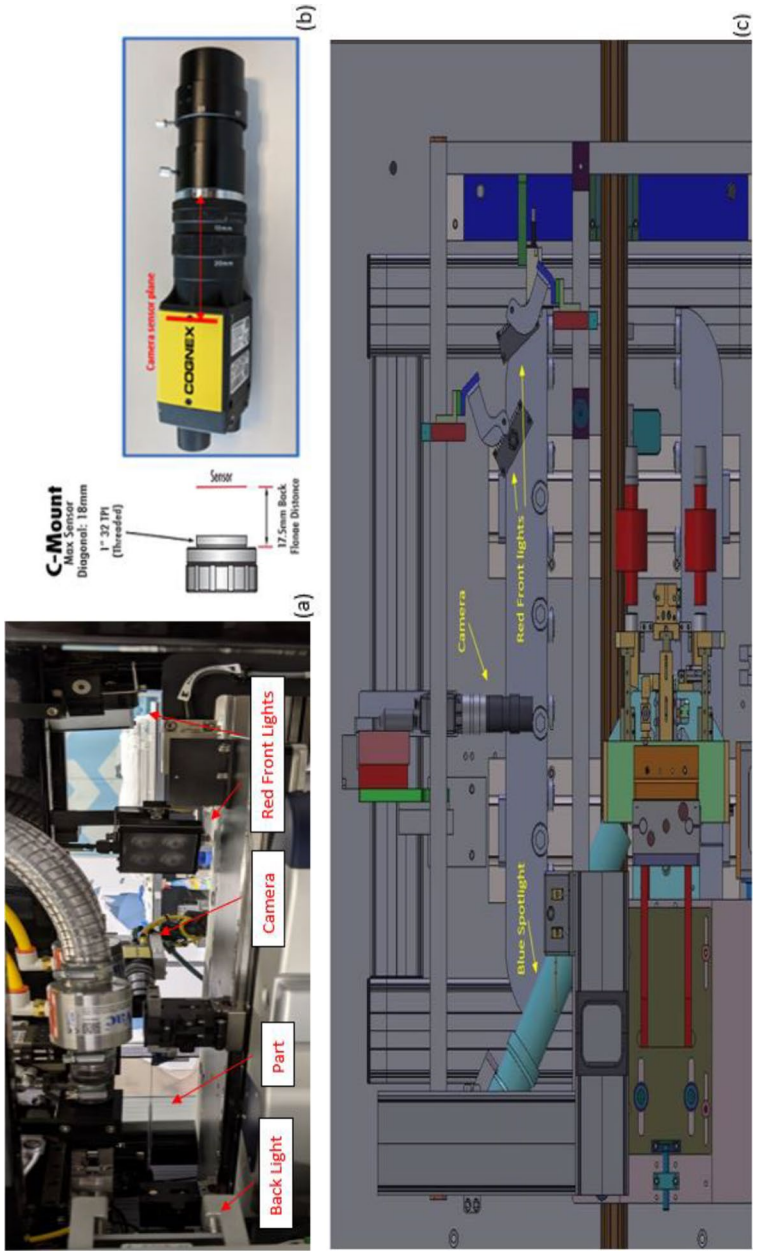

Fig. 13 **a** Test cell. **b** Camera and lens assembly. **c** Cell design layout

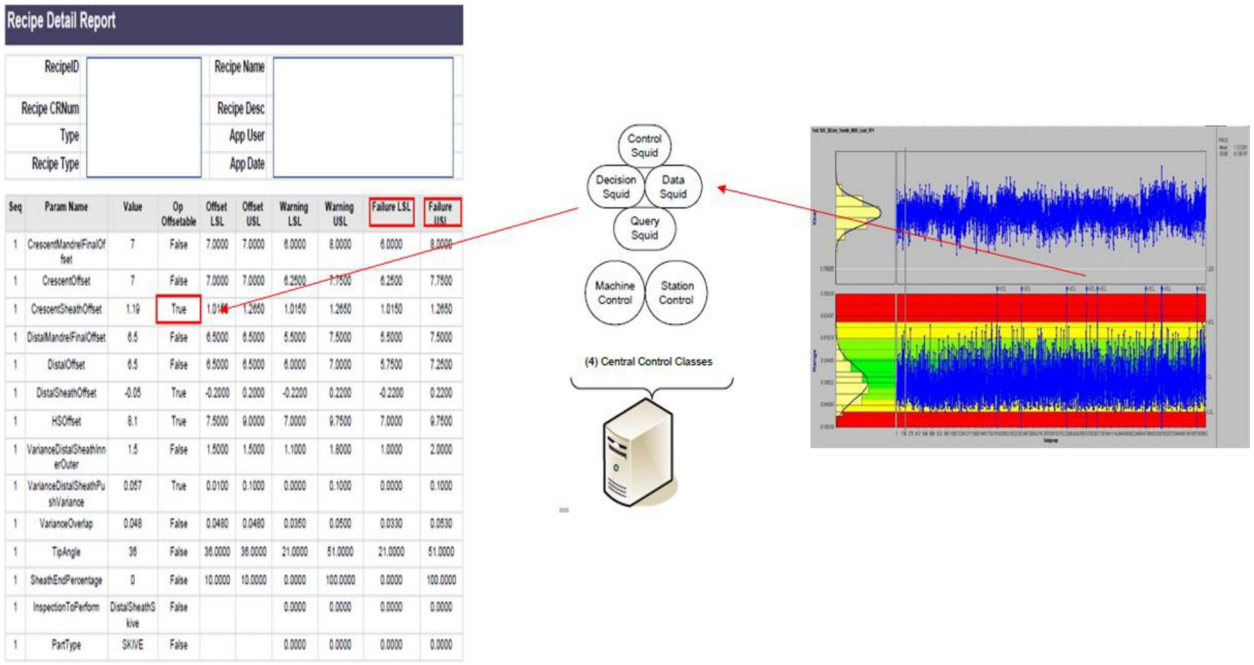

Fig. 14 Feedback loop 1: handling of out-of-control process by the system

Since the recipe management system is based on widely accepted industry ISA 88 standards, this becomes the fail safe for ensuring that no abnormal values are selected by the system inadvertently. This in turn ensures a high level of compliance and thus forms the basis of a regulatory pathway that is acceptable by the agencies. Similarly, for feedback loop 2, the system is restricted for making set up changes only within the validated range. For instance, during the laser bonding process, the collet servo that holds the part in from of the laser beam can be influenced by the output of the decision model. However, the out-of-limit instances are prevented by either a hard stop or by placing end-of-travel limit switches incorporated within the system hardware design.

Another instance is where the collet rotation is influenced to make sure all components are present and at their correct location. The decision model is designed to rotate the part or move it horizontally to try look for the features before rejecting the unit as a scrap (Fig. 15). The system in this instance is not attempting at all to influence the setup of the machine outside the range but only altering it within the range to address an out-of-control process.

The last element of the CPPS is real-time quality control and monitoring. The real-time manufacturing data collected through the vision system is passed onto the SPC client. SPC application in turn feeds this to the decision models for feedback loops 1 and 2 as shown above and also plots the final run data for the production floor staff (see Fig. 16).

This experiment has fully attained the goals of this research undertaking. The primary objective of the research was to automate the current manual oriented manufacturing process for the stent delivery catheters to an Industry 4.0 standard. The focus was to achieve flexibility at scale, real-time quality control and self-adaptability of the system. Adoption of the CPPS framework has demonstrated in full confidence that these objectives are achieved by the developed system even in a regulated industry setting. Full-scale deployment of the proposed system to all manufacturing worksteps will eliminate the need for inefficient destructive end-of-batch sampling towards a much efficient and leaner production process.

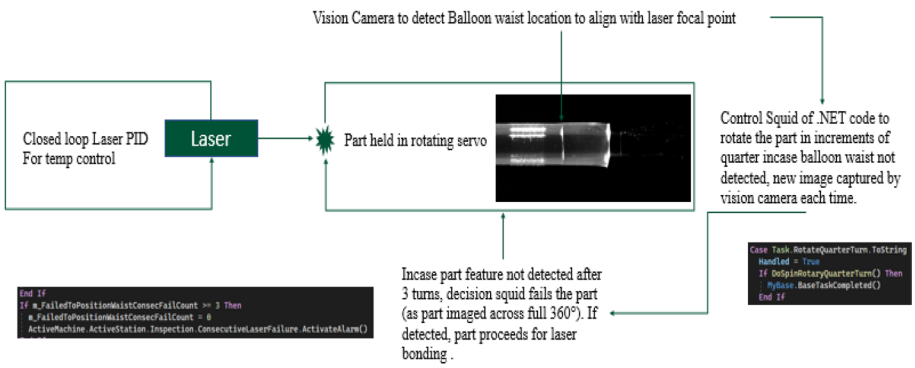

Fig. 15 Feedback loop 2: handling of out-of-control process by the system

Fig. 16 Real-time SPC monitoring for production floor staff

Conclusions

This paper focused on the current manufacturing challenges that are specific to the complex medical device manufacturing and aimed to address the issue of business conservatism around adoption of modern Industry 4.0 automation practices within such industries. The first step entailed understanding closely these challenges and breaking down the issues into smart problem goals. Then it investigated the available academic and scientific literature and real-world practices in other manufacturing industries, both regulated and non-regulated, to ascertain if these issues have been addressed previously. The result, some solutions were found either in practice or in theory in international standards or guidelines, that were then bootstrapped together in a way that the resultant proposal aims to serve the best interests of both these manufacturers and the regulatory bodies. The closed-loop CPPS model upon realization will be a benchmark in complex combinational class III biomedical device manufacturing, that will demonstrate the seamless integration of Industry 4.0 practices within highly regulated manufacturing environments. The model will enable the manufacturing process to move away from a destructive double sampling plan with a standard lot tolerance percent defective (LTPD) of 5% to an otherwise real-time 100% non-destructive verification of units, thus turning towards leaner production with higher outputs, best in-class quality and overall higher efficiencies of the process. Future research prospectives will include the amalgamation of this CPPS model to the top layer of the SMRM hierarchical model to the enterprise level. That will enable the system to be fully integrated with the other enterprise systems, key in regulated manufacturing environment, such as quality management system, calibration system, complaints management, customer feedback, supply chain management, planning, and forecasting. Once integrated with the top enterprise level, the proposed model will be fully in line with the Industry 4.0 standards and goals.

Abbreviations

3 V model	Volume, velocity, and variety
5C	Connection, conversion, cyber, cognition, and configuration
ADACOR	Adaptive holonic control architecture
ADR	Action design research
BDA	Big data analytics
CAD	Computer-aided design
CAM	Computer-aided manufacturing
CC	Cloud computing
CCIoT	Cloud computing and Internet of things
CEN	European Committee for Standardization
CFR	Code for Federal Regulations
CMfg	Cloud manufacturing
CNC	Computerized numerical control
CPP	Critical process parameters
CPPS	Cyber physical production systems
CPS	Cyber-physical systems
DCS	Data collection service
DMS	Data management service
DMSs	Dedicated manufacturing systems
DOE	Design of experiments
DT	Digital twin
EA	Enterprise architecture
EI	Enterprise integration
FDA	Food and Drug Administration
FMS	Flexible manufacturing systems
GAMP	Good automated manufacturing practice
HSTSM	Hierarchical spatial–temporal state machine
ICT	Information and Communication Technologies
IEC	International Electrotechnical Commission
IMSA	Intelligent manufacturing system architecture
IOT	Internet of things
ISA	International Society of Automation
ISO	International Standards Organization
IVRA	Industrial value chain reference architecture
JWG	Joint working group
LTPD	Lot tolerance percent defective
M2M	Machine to machine communication and interfaces
MCPS	Medical cyber physical system
MRI	Magnetic resonance imaging
OEE	Overall equipment efficiency
OPC UA	Open platform communication-unified architecture
OSGi	Open Service Gateway Initiative
PAT	Process analytical technologies and tools
PCA	Patient controlled analgesia
QMS	Quality management system
RAMI4.0	Reference Architecture Model for Industrie 4.0
RMAS	Reconfigurable manufacturing automation system
RMS	Reconfigurable manufacturing systems
RTRT	Real-time release testing
SMRM	Smart manufacturing reference model
SPC	Statistical process control
SSIF	Scandinavian Smart Industry Framework
URMSM	Unified reference model for smart manufacturing
VCPS	Vehicular cyber-physical systems

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Authors' contributions
All authors have contributed to this paper. BG is the primary author responsible for drafting, literature review and concept development. SM and JH are secondary authors for the article responsible for proof reading and peer review of the draft and getting the article submission ready. All authors have read and approved the final manuscript.

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