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Editorial

Expanding the Horizons of Manufacturing, towards Wide Integration, Smart System, and Tools

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This research topic aims at enterprise-wide modeling and optimization (EWMO) through the development and application of integrated modeling, simulation and optimization methodologies, and computer-aided tools for reliable and sustainable improvement opportunities within the entire manufacturing network (raw materials, production plants, distribution, retailers, and customers) and its components. Such an integrated approach incorporates information from the local basic control and supervisory modules into the scheduling/planning formulation, making it possible to react dynamically to incidents occurring in the network components at the appropriate decision-making level.

A wide-integrated solution should allow enhanced coordination and cooperation between network components by avoiding competition, eventually leading to local optima and inefficiency associated with inconsistent isolated decisions at different levels. Such a wide-integrated solution approach would provide new structural alternatives, more effective management policies, more economical design options. Moreover, the solution obtained can work in practice requiring fewer resources, emitting less waste, and allowing for better responsiveness to changing market requirements and operational variations, thus reducing cost, waste, energy consumption, environmental impact, and increased benefits.

More recently, the exploitation of new technology integration, such as through semantic models in formal knowledge models, allows capturing and utilizing domain knowledge, human knowledge, and expert knowledge towards comprehensive intelligent management. Otherwise, the development of advanced technologies and tools such as cyber-physical systems, the Internet of Things, the Industrial Internet of Things, artificial intelligence, big data, cloud computing, and blockchain, have captured the attention of manufacturing enterprises toward intelligent manufacturing systems. This Special Issue also calls for contributions from these advanced areas.

In summary, we look for articles addressing (but not limited to) the following concepts:

- the development of advanced mathematical models and methodologies for the integrated approach;
- the network design problem, such as the location of the plant, warehouses, and distribution centers, and capacity and technology selection;
- the supply chain planning problem, including distribution planning, inventory control, and product demand forecasting;
- the integration of production, financial and environmental aspects, risk, and uncertainty.

The expected models will tackle a multi-objective view of achieving the necessary trade-off between often contradictory benefits in terms of economic, environmental, customer satisfaction, and increased response to dynamic market changes:

- the development of detailed production scheduling at the plant level for batch, continuous and discrete manufacturing for online scheduling implemented in practice under real-time variations and uncertainty;

- the integration of the tracking system of network dynamics within the holistic decision-making model (e.g., by enclosing a model predictive control framework), thus facilitating equipment capacity handling similarly at strategic and operational levels and enabling adequate response to incidents for enhanced production sustainability;
- the development of suitable frameworks and algorithms for solving these problems in an efficient and integrated manner (e.g., surrogate problem decomposition, disjunctive programming, Lagrange decomposition);
- the development of software prototypes for the implementation of the above methodologies and algorithms, illustrating their applicability in several real-life industrial case studies involving typical manufacturing/distribution networks belonging to relevant sectors in the world;
- the development of novel frameworks focusing on the utilization of formal knowledge models, facilitating new technologies implementation, and transactional system integration;
- the further development of intelligent manufacturing systems for the transformation of manufacturing enterprises, from the traditional to the intellectualized;
- the development of intelligent systems and intelligent agents focused on cooperative work between human beings and computers, enhancing the capability of human decision-making and problem solutions in the process engineering field.

In the following, you will find selected contributions (original research, reviews, opinions, and perspectives) regarding this research topic. They bring novel solution approaches accompanied by rich case studies and examples of practical interest.

1. Original Research

The articles in this Special Issue examine different facets of enterprise-wide modeling and optimization through the development and application of integrated modeling, simulation and optimization methodologies, and computer-aided tools for reliable and sustainable improvement opportunities within the entire manufacturing network.

The contribution by David Bogle et al. [1] addresses the present and future situation of the high complexity inherent with batch manufacturing of many products. The intrinsic flexibility associated with batch manufacturing has been the choice of most pharma products manufacturing. As a result, it is usual to see a battery of batch reactors in the pharma industry or single batch reactors with high and complex inlet and outlet pipe connections, some of them unused, because different or new products appear in the industry portfolio. The net result is increasing the cost of the final product. Instead, this original paper offers a novel approach: The use of operational envelopes to study the trade-off between the design and operational flexibility of a tablet manufacturing process. Moreover, using an alternative adaptive sampling technique will alleviate the significant computational burden associated with the operational envelopes. Finally, a critical fluidized bed dryer case study at the heart of the continuous manufacturing of tablets supports the paradigm shift change to continuous manufacturing.

The paper by M. Ziyan Sheriff et al. [2] also examines the transition from batch to continuous processes in the pharmaceutical industry. In order to enable the quality-by-control (QbC) paradigm to move forward, this work developed and presented a moving horizon estimation-based nonlinear model predictive control (MHE-NMPC) framework to accomplish the dual requirement of accurate estimation and efficient control. The real-time implementation feasibility of the developed framework was also discussed, and the ability of the proposed framework to solve the optimization problem at each time step in a manner that enabled real-time implementation was highlighted. The practical applicability of the developed framework was corroborated through two realistic case studies that incorporated the effects of glidant to better control CQAs such as the tensile strength. Both examples demonstrated the ability of the framework to achieve reasonable control performance despite the presence of varying sources and degrees of plant model mismatch.

The work by Zixue Guo et al. [3] proposes an evaluation model that addresses the problem of fuzziness and randomness in regional logistics decarbonization, assessing its development. An evaluation index contemplates three dimensions: low-carbon logistics environment support, low-carbon logistics strength, and low-carbon logistics potential. Secondly, the evaluation indexes serve as cloud model variables, and the cloud model theory determines numerical characteristic values and cloud affiliation degrees. Finally, the entropy weight method determines the index weights and calculates the comprehensive determination degree of the research object affiliated with the logistics decarbonization level. Finally, the Beijing–Tianjin–Hebei region is the example used for empirical evidence, analyzing the development of logistics decarbonization and its temporal variability in Beijing, Tianjin, and Hebei provinces and cities. The study results show that the development of logistics decarbonization in Beijing, Tianjin, and Hebei Province has improved to different degrees from 2013–2019, but the development is uneven. Developing to 2019, the three provinces and cities of Beijing, Tianjin, and Hebei still have significant differences in terms of the economic environment, logistics industry scale, logistics industry inputs and outputs, and technical support.

In their article, Vivek Dua et al. [4] aim to introduce a method for designing multi set-point explicit controllers for nonlinear systems through recent advances in multi-parametric programming. Multi-parametric programming (mp-P) has received considerable attention from the process systems engineering community because of its unique ability to aid in the design of explicit model predictive controllers and thus shift the computational burden associated with offline control. The authors examine a case of multi-parametric nonlinear programs (mp-NLPs) that involve both endogenous uncertainties, in the form of left-hand side parameters (LHS), as well as exogenous uncertainty in the cost coefficient of the objective function (OFC), and, on the right-hand side of the constraints (RHS), uncertain parameters on the right-hand side (RHS). In engineering problems, LHS uncertainty arises from variations in model coefficients, due to parameter estimation errors or model mismatch; OFC uncertainty arises due to fluctuation in market prices or control penalties while RHS uncertainty can be due to varying system exogenous factors. The contribution of the present work is a novel framework for the design of multi set-point explicit controllers for nonlinear process systems.

As a demarcation of the past, present and future of intelligent systems, a Tri-X Intelligence (T.I.) model is proposed in this paper by Baicun Wang et al. [5] to state the mechanism, factors, and connotation of three main entities (conscious humans, physical objects, and cyber entities), including single-X intelligence, two-X integrated intelligence, and three-X complex intelligence. Every single entity shows primitive intelligence. Two-entity integration creates integrated intelligence. Three-entity fusion generates advanced intelligence. The intelligentization mechanism of artificial systems continuously converts human intelligence to machine intelligence via different channels and interfaces. With the increasing use of machine intelligence, humans will gradually play a less significant role in intelligent systems. However, human intelligence will keep influencing artificial systems in the form of software/algorithms to drive intelligent systems. Therefore, we cannot take humans out of the systems given the accelerating development of technology. The key to success is to adapt humans to new work environments, i.e., not to replace but to enhance. According to the Tri-X Intelligence (T.I.) model, humans need to think more about how to collaborate with cyber systems rather than with intelligent systems, a Tri-X Intel than training operators to work like computers. The proposed Tri-X model (e.g., Human-Cyber-Physical-System HCPS) will integrate the intelligence in the complex system with a combination of human-cyber-physical and machine subsystems.

In addition, Sujeon Baek et al. [6] prepared a testbed for conducting a pick-up operation using a vacuum gripper with a single suction cup. Using the proposed method, the air pressure in the Venturi line was automatically monitored in real-time. When a command for starting suction was provided to the gripper, a sharp decrease in the collected air pressure signals appeared at approximately 0.5 s. However, the same decline was not observed in the signal for faulty box surfaces; consequently, the suction action and the corresponding gripper operation were not performed owing to insufficient contact between the suction cup(s) and the contact surface of the object. Using the early detection results derived from the air pressure signal analysis, a prediction-based process adjustment method for the pick-up operation was proposed. Through pick-up experiments using the developed testbed, it was revealed that the z-position of the suction cup significantly affects whether an object is gripped adequately by the vacuum gripper or not. Therefore, it is possible to determine a possible error situation in advance (before the failure of the lifting operation) and provide appropriate feedback control commands so that the target operation is finished successfully without stopping machine operations.

The process, manufacturing, and service industries face many non-trivial challenges in a customized market environment, from product conception, design, development, commercialization, and delivery. Thus, industries can benefit by integrating new technologies into their day-by-day tasks gaining companies profitability. Puigjaner et al. [7] present an integrated model framework for enterprise process development activities called a "Comprehensive intelligent management architecture model for integrating new technologies for services, processes, and manufacturing who strive for finding the most efficient way towards enterprise and process intelligence." The model comprises and structures three critical systems: process, knowledge, and transactional. As a result, analytical tools belonging to process activities and transactional data systems are guided by a systematic development framework consolidated with formal knowledge models. Thus, the model improves the interaction among processes lifecycle, analytical models, transactional systems, and knowledge. Finally, a case study systematically presents an acrylic fiber production plant applying the proposed model, demonstrating how the three models described in the methodology work together to systematically achieve the desired technology application of life cycle assessment. The results conclude that the interaction between the semantics of formal knowledge models and the processes-transactional system development framework facilitates and simplifies new technology implementation along with enterprise development activities.

Compared with other fossil fuels, natural gas (N.G.) is considered a sustainable and potential energy source in the future. Being liquefied, natural gas (LNG) is 600 times smaller than the gaseous state of N.G., LNG becomes especially attractive if obtained at a competitive cost. The authors of this article, Liang Zhao et al. [8], show that modeling and optimizing the LNG terminals may also reduce energy consumption and GHG emissions. In this work, the authors propose an operational optimization model of the LNG terminal to minimize the energy consumption of boil-off gas (BOG) compressors and low pressure (L.P.) pumps. Finally, an MINLP model determines whether the pumps are running or on standby, and the number of compressor level chosen as a binary variable. The model can propose operating strategies for varied flow rates of the send-out speed, and the ambient temperature can be offered using the model. An actual case study on the LNG terminal is presented to indicate the effectiveness of the proposed approach. Finally, the optimization model provides the minimum energy consumption and the corresponding decision variables. The optimized compressor load and recirculation flow rate were 8.44 t/h and 122.58 t/h, respectively. Compared with the previous period, 26.1% of energy can be saved after optimization. About 16.21% of energy consumption can be saved annually.

In his challenging article, Heinz A. Preisig [9] presents "Reductionism and splitting application domain into disciplines and identifying the smallest required model-granules, termed "basic entity" combined with systematic construction of the basic entities, yields a systematic approach to process modeling." They do not aim toward a single modeling domain, but enabling specific application domains and object inheritances to be addressed. They start with reductionism and demonstrate how the basic entities depend on the targeted application domain. They use directed graphs to capture process models, and introduce a new concept, which they call "tokens," that enables the extension of the context beyond physical systems. The network representation is hierarchical to capture complex systems. The interacting basic entities are defined in the leave nodes of the hierarchy, making the overall model the interacting networks in the leave nodes. Multi-disciplinary and multi-scale models result in a web of networks. They identify two distinct network communication ports, namely, ports that exchange tokens and ports that transfer information of tokens in accumulators. An ontology captures the structural elements and the applicable rules and defines the syntax to establish the behavior equations. Linking the behaviors to the fundamental entities defines the alphabet of a graphical language. They use this graphic language to represent processes which have proven to be efficient and valuable. Then, a set of three examples demonstrates the power of graphical language. Finally, the Process Modelling framework (ProMo) implements an ontology-centered approach to process modeling and uses graphic vocabulary to construct process models.

In this article, Ignacio Grossmann et al. [10] address an inventory management problem for a make-to-order supply chain with inventory holding and-or manufacturing locations at each node. The lead times between nodes and production capacity limits are heterogeneous across the network. This study focuses on a single product, a multi-period centralized system in which a retailer is subject to uncertain stationary consumer demand at each time period. The authors consider two sales scenarios for unfulfilled demand: backlogging or lost sales. The daily inventory replenishment requests from immediate suppliers throughout the network are modeled and optimized using three different approaches: (1) deterministic linear programming, (2) multi-stage stochastic linear programming, and (3) reinforcement learning. The performance of the three methods is compared and contrasted in terms of profit (reward), service level, and inventory profiles throughout the supply chain. The proposed optimization strategies testing occurs in a stochastic simulation environment built upon the open-source OR-Gym Python package. The results indicate that stochastic modeling yields the most significant increase in profit of the three approaches. In contrast, reinforcement learning creates more balanced inventory policies that would potentially respond well to network disruptions. Furthermore, deterministic models perform well in determining dynamic reorder policies comparable to reinforcement learning in terms of their profitability.

In an inspiring novel article, Zeinab Shahbazi and Yung-Cheol Byun [11] bring the latest developments and experimental results on smart manufacturing. The modern industry, production, and manufacturing core is developed based on smart manufacturing (S.M.) systems and digitalization. Smart manufacturing's practical and meaningful design follows data, information, and operational technology through the blockchain, edge computing, and machine learning to develop and facilitate the smart manufacturing system. This process's proposed intelligent manufacturing system considers the integration of blockchain, edge computing, and machine learning approaches. Edge computing balances the computational workload and similarly provides a timely response for the devices. Blockchain technology utilizes the data transmission and the manufacturing system's transactions, and the machine learning approach provides advanced data analysis for a vast manufacturing dataset. Finally, the model solves the problems using a swarm intelligence-based method regarding intelligent manufacturing systems' computational environments. The experimental results present the edge computing mechanism and similarly improve the processing time of a large number of tasks in the manufacturing system.

Present increasing regulatory demands force the pharmaceutical industry to invest its available resources carefully. That is especially challenging for small and middle-sized companies. For example, computer simulation software such as FlexSim allows one to explore variations in production processes without interrupting the running process. Claus-Michael Lehr et al. [12] applied a discrete-event simulation to two approved film-coated tablet production processes in this article. The simulations were performed with FlexSim (FlexSim Deutschland, Ingenieurbüro für Simulationsdienstleistung Ralf Gruber, Kirchlengern, Germany). Process visualization required the use of Cmap Tools (Florida Institute for Human and Machine Cognition, Pensacola FL, USA), and statistical analysis used MiniTab® (Minitab GmbH, Munich, Germany). The most critical elements identified during model building were the model logic, operating schedule, and processing times.

These factors required graphically and statistically verification. In addition, employee utilization optimization required three different shift systems to be simulated, revealing the advantages of two-shift and one-and-a-half-shift systems compared to a one-shift system. Finally, without interrupting any currently running production processes, we found that changing the shift system could save 50–53% of the campaign duration and 9–14% of the labor costs. In summary, we demonstrated that FlexSim, mainly used in logistics, can also be advantageous for modeling and optimizing pharmaceutical production processes.

Tibor Krenicky et al. [13] present a study on the surface quality dependency on the selected parameters of cuts made in Hardox by abrasive water jet (AWJ). The authors applied the regression process to measured data and prepared the Ra and Rz roughness parameters equation. One set of regression equations describes the relationship of Ra and Rz on cutting parameters—pumping pressure, traverse speed, and abrasive mass flow rate. The second set of regression equations describes relationships between the declination angle in kerf as the independent variable and the Ra or the Rz parameters as dependent variables. Finally, the models can predict cutting variables to predict the surface quality parameters.

The complexity of the automated guided vehicles (AGV) system requires substantial decision-making and is challenging to solve. The authors Adrian Kampa et al. [14], use the flexible manufacturing system solution with the associated AGV transport system and discuss such systems' design and simulation issues. The initial system design optimization stage is crucial, and computer simulation enables relatively easy elaboration and testing of various manufacturing and logistics systems variants. On the other hand, excessive simplifications may appear applied at the modeling stage, making the simulation not reflect the production system properly. On the other hand, it is worth noticing that detailed modeling is very labor-intensive and requires the involvement of experienced specialists. Therefore, choosing which parameters to use in the modeling process and which metric to evaluate the model. Finally, to make the simulation more accurate and assess the system's productivity, the authors propose using overall equipment effectiveness (OEE) metrics. The results obtained from the presented simulations show that the OEE metrics may be helpful in the modeling and productivity evaluation of manufacturing and logistics systems, with the generalization of overall factory effectiveness (OFE) and overall transport effectiveness (OTE). The use of OEE factors also allows for comparison of the results obtained from different manufacturing systems. For example, many of them with OEE scores lower than 45% in the real world and a small number of world-class companies have an OEE value higher than 85%. Accordingly, the simulation results can also be helpful in analyzing the costs involved in implementing a given project and at the stage of the in-depth design of the production system.

The following work addresses the closed-loop stability problem with an application to refinery preheats trains' online cleaning schedule stability problem under fouling. Lozano Santamaría and Sandro Macchietto [15] focus on the sources of instability and ways to mitigate it. The various metrics developed to quantify schedule instability for online scheduling account for distinct aspects, such as changes in task allocation, task sequence, starting time of the task, and the earlier or later occurrence of such changes in the future scheduling horizon. Based on the proposed methods, further stability metric variations could be quickly developed (for example, ways of assigning weights to distinct contributions to a schedule change). These stability considerations can be practically and, in a rather general way, introduced in a closed-loop nonlinear model predictive control (NMPC) formulation of the optimal scheduling and control problem and solved online over a moving horizon, in terms of penalties in an economic objective or via additional constraints. The above methods demonstrated to be helpful for the online cleaning scheduling and flow control of refinery preheat trains, a challenging application with significant economic, safety, and environmental impact. A demanding industrial case study followed an illustrative, small but realistic case study. Results show that, of the three alternatives evaluated, the terminal cost penalty proved to be inefficient in this case. The other two (fixing some predictions horizon decisions and penalizing schedule changes between consecutive evaluations) improved the closed-loop schedule stability against various economic penalties. The results highlight the importance of including stability considerations in an economically oriented online scheduling problem to obtain feasible solutions for operators over long operating horizons without sacrificing the benefits of a reactive system to reject disturbances or take advantage of them. The application of the metrics developed in this manuscript is not restrictive to the specific closed-loop NMPC scheduling implementation detailed here. They are helpful to assess schedule stability in general regardless of how schedules are calculated, only relying on the existence of two consecutive evaluations or predictions of the schedule within a common period. The two successive instances may have different control horizons, scheduling horizons, or update frequency. Lastly, although this work dealt with a specific application (the optimization of refinery heat exchanger networks subject to fouling), the formulations and solution approach demonstrated here should apply to important systems, such as batch and semi-continuous processes.

Mohammed Alkahtani et al. [16] enlighten the management of the man-machine interaction as essential to achieving a competitive advantage among production firms and specifically more highlighted in the case of processing agricultural products. The authors design a non-derivative technique to integrate an algebraic approach in the agri-product based supply chain to optimize the resources and coup with variable demands through a controllable production rate. The analysis provides a platform for manufacturing managers to invest in advanced technology in agricultural supply chain management (agri-SCM), leading to a less rejection production environment for clean manufacturing. The solution methodology of the proposed model included manufacturing limitations in the integration of the objective formulations with the developed system. The authors use sensitivity analysis to evaluate sensitivity for an optimal solution to the value of uncertain parameters, providing confidence in the model's resolution. Managerial insights are beneficial to agricultural supply chain management (agri-SCM) for the agri-food processing industry, and the people with cleaner production and carbon emission prioritized policies. The authors can extend the research into a three-echelon agri-SCM model by considering the farming industry and agri-retailer. The fuzzy set theorems can deal with costs, prices, inflation, and time value uncertain factors. Finally, the authors envisage a feasible conversion of the deterministic model into probabilistic or stochastic theorems for application in real scenarios. Overall, the agri-product supply chain requires global development to make food more secure and accessible.

In the following article, Dejan Gradišar and Miha Glavan [17] consider a manufacturing problem requirement plan. This plan must satisfy the capacity needs and be available by the work order's due date. In addition to this, the program must also consider a group of work orders to produce from the same batch of raw material. In this way, the manufacturer can systematically compensate for some undesirable variations in raw material quality. In day-to-day practice, the plan management makes it challenging to maintain the plan up-to-date, even in smaller dimensions. As a result, the operator's decisions are time-consuming and prone to errors. That results in situations in which the operator must constantly make plan corrections. Finally, this paper proposes using an extended bin-packing problem formulation to solve the material planning systematically. Finally, a fundamental bin-packing problem (BPP) formulation requires an extension to include constraints such as variable bin and item sizes. For example, one can use time limitations and only a group of bins to produce one group of items. The suggested solution offers a tool for supporting the production planner's decisions. With it, they can determine how to efficiently cut the raw material to satisfy the planned work orders. Depending on the situation, the planner can choose between various model formulations. Additionally, they can optimize the leftover, tardiness, or both. Finally, we demonstrated that the proposed solution could quickly solve a problem of realistic dimensions to be of use in an industrial application. However, case-specific requirements would first need to be analyzed to prioritize the importance of leftovers and/or tardiness in real applications.

Andrzej Paszkiewicz et al. [18] propose a novel approach for integrating the distributed additive manufacturing process enabling remote designing, selecting appropriate manufacturing means, and implementing a physical production process and control at all stages. This approach was possible thanks to the development of an unprecedented framework. The authors integrated distributed and functionally different elements (Informative Technology (I.T.) and manufacturing), forming a coherent design and manufacturing system. Importantly, this framework ensures an increase in production efficiency, shortens production time, reduces costs, and increases flexibility and accessibility to the latest methods and design and manufacturing tools. In addition, they presented a mechanism that facilitates the integration of independent manufacturing environments by considering and implementing appropriate levels of maturity in the system. The implementation in a natural production environment, i.e., at Infosoftware Poland, confirms the proposed solution's validity. At present, work is in progress to integrate the rapid prototyping laboratory of the Rzeszów University of Technology. In addition, the automotive and aerospace industries can widely use the presented platform. In addition, it will facilitate cooperation between industrial clusters and academic centers to a higher degree and encourage collaboration between small enterprises and startups. Finally, from the perspective of management, the technical implementation of the presented framework allows one to adapt to the needs of globalization and facilitates the integration of distributed resources. Thus, this framework affects business, logistics, and technological processes. One of the implications of implementing such a framework is the need to develop or adapt existing workflows to the new heterogeneous and distributed work environment.

2. Review

The review by Marianthi Ierapetritou et al. [19] informs the reader of the latest development and application of emerging technologies of Industry 4.0, enabling the realization of digital twins (D.T.). D.T.s is a crucial development of the close integration of manufacturing information and physical resources that raise much attention across industries. The critical parts of a fully developed D.T. include the physical and virtual components and the interlinked data communication channels. Following the development of Internet of Things (IoT) technologies, there are many applications of D.T. in various industries, but the progress is lagging for pharmaceutical and biopharmaceutical manufacturing. This review paper summarizes the current state of D.T. in the two application scenarios, providing insights to stakeholders and highlighting possible challenges and solutions to implementing a fully integrated D.T. In pharmaceutical manufacturing, building blocks of a D.T., including process analytical technology (PAT) methods, data management systems, unit operations, flowsheet models, system analyses methods, and integration approaches, have all been developed in the last few years, but gaps in PAT accuracy, real-time model computation, model maintenance capabilities, real-time data communication, as well as concerns in data security and confidentiality, are preventing the full integration of all the components. Several insights seem appropriate to solve these challenges. First, developing new tools such as near-infrared spectroscopy (NIRS) and in-line U.V. spectroscopy, iterative optimization technologies, and different online adaptive methodologies can help resolve the existing issues in PAT methods. Second, efficient algorithms and reduced-order modeling approaches need further study for process models to reduce simulation time to achieve real-time computation. Third, adaptive modeling methods with online streaming data will be under further investigation in model maintenance. Third, to have a fully integrated and automated D.T., the information flow from the virtual component to the physical plant also must be established. Moreover, the virtual plant should be able to change system settings and control the physical plant to help achieve an optimized process within the design space. Ideally, all these components require appropriate physical and virtual security protocols.

3. Opinion

In the past few years, pharmaceutical products have evolved toward disease- and patient-specific therapeutics involving meticulous manufacturing steps. In addition, cell-based therapeutics and vaccines present high sensitivity to environmental and transport conditions, complicating supply chain logistics. Increased drug specificity and demand uncertainty add further complexity to the design and operation of robust manufacturing processes and distribution networks. As Maria M. Papathanasiou et al. [20] discuss in their paper, the pharmaceutical industry has taken significant steps toward improving existing and-or developing novel processes that promise agile, responsive, and reproducible manufacturing. Similarly, distribution networks in the pharmaceutical sector are undergoing a paradigm shift, exploring the capabilities of decentralized models. Such developments accompany digital innovation in the pharmaceutical industry that enables seamless communication between process units, production plants, and distribution nodes. As discussed earlier, process systems engineering has been at the forefront of allowing digitalization through the development of computer modeling tools. The latter can assist with real-time monitoring of critical storage conditions for sensitive pharmaceutical products with short shelf-life, thus increasing drug safety. One of the main challenges hindering the fast exploitation of Industry 4.0 principles in pharmaceutical manufacturing is a mindset change. Practitioners should embrace the benefits arising from the realization of Pharma 4.0 towards replacing paper-based systems with cloud-based servers. That will allow significantly improved agility and productivity in the operations of the pharmaceutical sector.

4. Perspective

The authors of the perspective, Krist V. Gernaey et al. [21], emphasize that despite the benefits of continuous over-batch bioprocessing, its adoption has lagged, with few exceptions. However, the batch manufacturing paradigm's dominance in the industry for reasons such as "batch processing is familiar and works very well" cannot be sustained in the long term, given the new biomanufacturing challenges. Moreover, the industry-held perception of complexity in continuous bioprocessing is becoming obsolete as more and more new technologies and solutions continually improve the situation. Several academic- and industry-led consortia are working to improve the perception regarding continuous bioprocessing by bringing the questions to the correct stakeholders who can address them. The training provided by these initiatives to the top management of the companies is playing an essential role in changing the perception and, at the same time, also creating new scientists and operators that can understand and respond to a new set of operational challenges. However, wider adoption of continuous bioprocessing will only be possible if the technical, management, and regulatory gaps are acknowledged. This paper argues that concerted efforts focusing on technology, management, and regulatory aspects are abridging them.

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