Discrete Event Simulation Approach for Pharmaceutical Industry Calibration Laboratory Service Digital Twin Model

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ABSTRACT

This research aims to develop a simulation theory using discrete event simulation as a convincing tool for building a digital twin models in the pharmaceutical industry calibration department as part of the supporting components enabler for industry 4.0.

The Methodology used are define the Calibration Laboratory service model, then analyze the big data collected from the service performance parameters. The analyzed data will be used to continue the development of discrete event simulation models for calibration laboratory service systems using ProModel2016 software. The simulation output data will be verified with real event data to ensure similarity.

The study finds that the Discrete Event Simulation approach can be used as a convincing tool to develop digital twin models as virtual replicas of Calibration Laboratory Services in the Pharmaceutical Industry so that improvement planning can be analyzed efficiently.

There is a limitation of this research that the digital twin model can only be verified for the Pharmaceutical Industry Calibration Laboratory Services as a case study object. Further research needs to be carried out to expand the possibilities of using this discrete event simulation approach for Digital Twin Model in every aspect of industrial activities.

KEYWORDS

Discrete Event Simulation, Digital Twin, Industry 4.0, Pharmaceutical Industry, Calibration laboratory

INTRODUCTION

The pharmaceutical industry is one of the industrial groups that is highly regulated and strickly supervised by state authorities. Pharmaceutical manufacturing practices for making medicinal products must comply with GMP (Good Manufacturing Practices) provisions, both international standards (PIC/S, 2021) and national standards as outlined in the CPOB (*Cara Pembuatan Obat yang Baik*) Regulations (BPOM, 2024). This is done to ensure drug quality and protect the safety of patients as drug consumers.

One of the activities that must be carried out by industry is to ensure the accuracy of all measuring instruments involved in the drug manufacturing process, both process parameter measuring instruments and product quality testing equipment. This activity is known as Calibration. Each measuring instrument is deeply reviewed with a risk assessment to determine the calibration period interval. One of the things that every pharmaceutical industry must strive for is to minimize the number of measuring instruments that have not been calibrated after its due date determination. Because this can cause the process to stop until calibration is carried out.

However, the pharmaceutical industry is also required to be competitive in carrying out its organizational activities so that it can produce affordable products for drug users. The smooth supply chain of industrial activities is important, not only in core business activities, but also involves all supporting departments in the internal organization, such as calibration service, as part of the entire supply chain that must be studied in order to obtain optimum operational conditions (Shah, 2004).

The complexity in today's industry is exploding. New production methods, miniaturization of electronics, novel sensor technologies, and the internet of things (IoT) have led to many disruptive developments which is known as Industry 4.0 evolution. As a consequence of these evolutions, the number of complex components and systems is ever-increasing. This leads to more complex products, offering unique opportunities in terms of efficiency or autonomy of components and systems. Workflow and production systems, design and engineering, components and products, interaction between companies and clients, supply chains, and much more, everything will benefit from wide deployment of computer science, systems theory, model-based design, and data-driven approaches. Novel technology trends can disrupt many paradigms and change whole industries (Hartmann & van der Auweraer, 2020).

The Digital Twin (DT) concept was originally introduced in 2003 by Michael Grieves and first made public by NASA in 2012. Now, it is considered among the most promising new trends in the high-tech industry. The DT is defined as a virtual replica of a physical asset. It integrates all information generated during the life-time of a product; pre-existence, during existence, and post-existence. The DT bridges the virtual and real world with the goal to model, understand, predict, and optimize the behavior of real assets. The DT promise to speed-up design even further and at the same time drastically reduce lifetime costs of complex high-tech systems and thus likely gain a significant competitive advantage. DTs are considered highly important to business and have been named among Gartner's Top 10 Strategic Technology Trends. It is expected that they will lead to high savings along the whole life-cycle, often several times the initial asset investment. DTs allow for novel services such as on-site diagnostics, operation optimization, rehabilitations, and component sales instead of total asset sale (Wu et al., 2023).

Discrete event simulation models are designed to simulate the operation of a system as a discrete sequence of events, where each event occurs at a specific point in time and

changes the state of the system. This approach allows for the representation of various system components, their interactions, and the flow of materials or information through the system (Park et al., 2024).

The integration of digital twins and discrete event simulation models has emerged as a powerful approach in the realm of complex systems analysis and optimization. One of the core aspects of a digital twin is the integration of modeling and simulation techniques, which can provide valuable insights into the behavior and performance of the physical system. Discrete event simulation models are particularly well-suited for this purpose, as they can capture the dynamic and stochastic nature of complex systems (Thelen et al., 2022).

Initial DTs modeling in the calibration department of one of the leading pharmaceutical industries in Indonesia has been carried out using the discrete event simulation method which can be developed into an initial DTs model in 2021 (Amrih & Laksono, 2024). The Pharmaceutical Industry then uses simulation analysis to make improvements through investment in increasing the capacity of In-Lab calibration facilities in 2023, and increasing calibration objects that must be managed from 5536 instruments in 2021 to 7319 instruments in 2023 (32.2% increase in 2 years). A review of the discrete event simulation models that have been developed needs to be carried out to sharpen the similarity and optimization behavior of service system calibration as a refinement of the Digital Twin model.

RESEARCH METHOD

The method used in this research consists of the following steps:

- Re-define Calibration Laboratory model design from the previous research (Amrih & Laksono, 2024).
- Big data collection at The calibration laboratory performance record data from July 2023 to December 2023, and statistical distribution fitting using Minitab2019 on every step of the model.
- Re-develop discrete-event simulation model for the calibration laboratory service system. The simulation model to be created using ProModel2016 software.
- Verify the simulation model by statistical significance similarity approach using one sample t-test between actual event output parameters and several simulation replications that were built.

Figure 1 shows the flow of the calibration service process that occurs. Starting from a request for a Calibration Order (CalOrd). Calibration order can be an automatic command from the calibration management computer system for the implementation of periodic calibrations according to the specified calibration time interval, or an order that is requested from the user randomly based on the user's needs and requirements. CalOrd is received at the administration desk (Adm Desk) and then forwarded to the Technician Desk (Tech Desk) electronically.

Technician will take CalOrd to get calibration data. There are 2 groups of calibration tasks: Calibration tasks in the calibration laboratory (InLab), where there is a waiting time for sending instruments from the user to the calibration laboratory, and waiting time for the calibrators availability, and the task of calibration at on-site calibration which includes a waiting time until the equipment shuts down so that calibration can be carried out and also a waiting time for the calibrator availability. In the case of this pharmaceutical industry, for the on-site calibration group, divided into 3 groups based on the clustering of travel time required from the Tech Desk to locations with different building groups categorized into:

Pharmaceutical product plants (Onsite Phrm), Herbal product plants (Onsite Herbs) and plant category for Food Supplement (Onsite Food).

While waiting for instrument availability and calibrator availability, technicians are randomly free to perform calibration work for other CalOrds with priority on the first due date for the recalibration of the instrument.

The loading time for calibration based on time measurement samples has a certain data distribution pattern. Then after the calibration process, the CalOrd entities turn into calibration data (CalData) to be brought by resource (technicians) to the Adm Desk, processed and ratified into a Calibration Certificate (CalCert). Entities that have changed to CalCert are then sent to users in softcopy and distributed electronically.

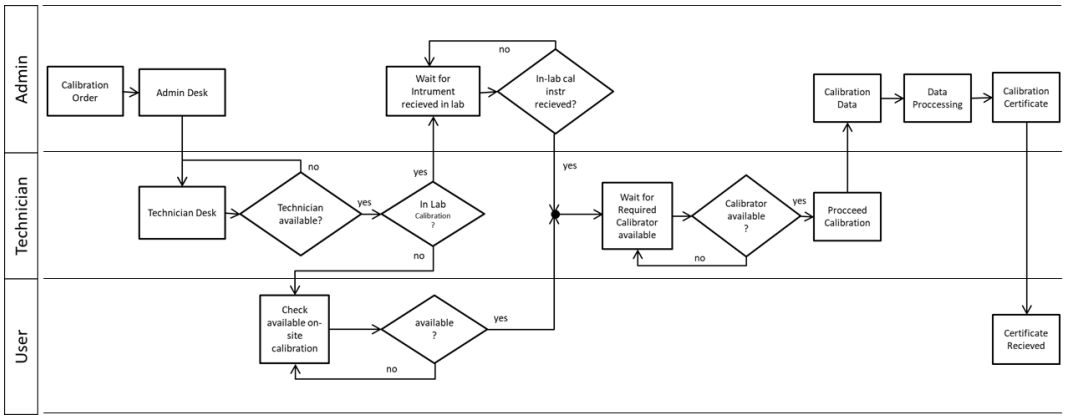

Figure 1. Calibration Service Model

Data analysis was carried out over a range of calibration activities between 1 July 2023 to 31 December 2023, with a total of 4643 calibration activities. Distribution fit was carried out to infer the CalOrd pattern using Minitab2019 software as depicted in Figure 2 below. Distribution fit for each month shows the most suitable Weibull distribution pattern.

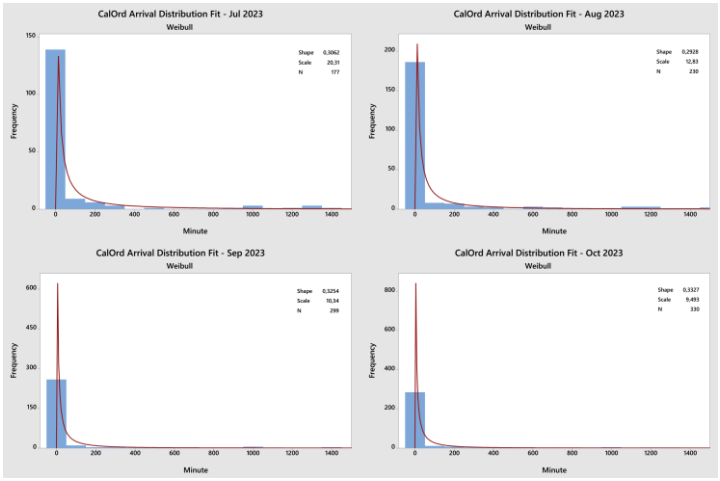

Figure 2. Distribution Fit for CalOrd Arrival from July to October 2023

Time measurement examples of the delays can be seen on Figure 3. This time is considered as a waiting time, wait for instrument to be calibrated available (received in the calibration lab for In-lab Calibration or instrument at the shut down status for On-site

calibration) and wait for the calibrator used available. And the calibration activities duration time data analysis can be seen at Figure 4. All data also have to be analyzed for the goodness of fit test distribution. The Probability among InLab Calibration, Onsite Phrm, OnsiteFood and OnsiteHerbs as shown at Figure 5.

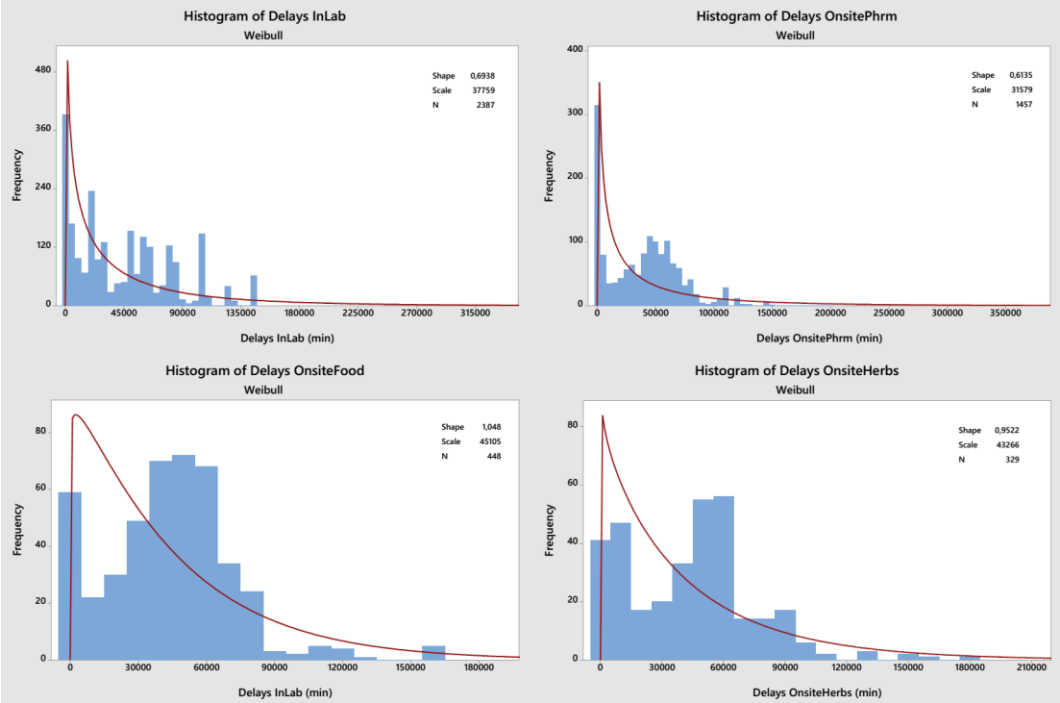

Figure 3. Delays time distribution fitting

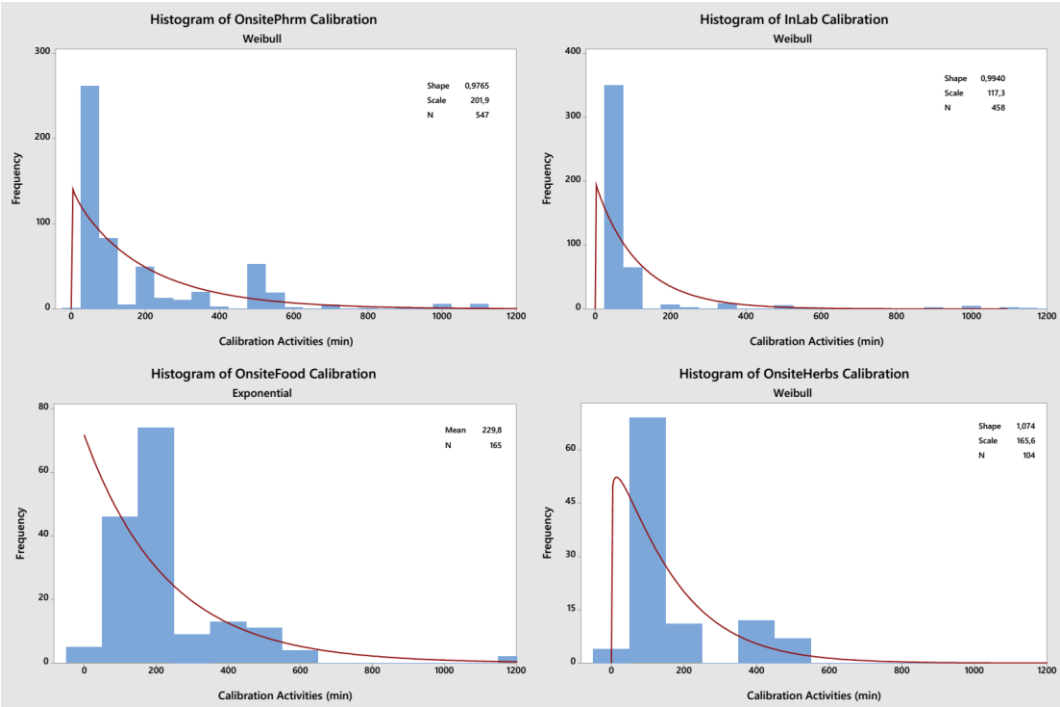

Figure 4. Calibration activities time distribution fitting

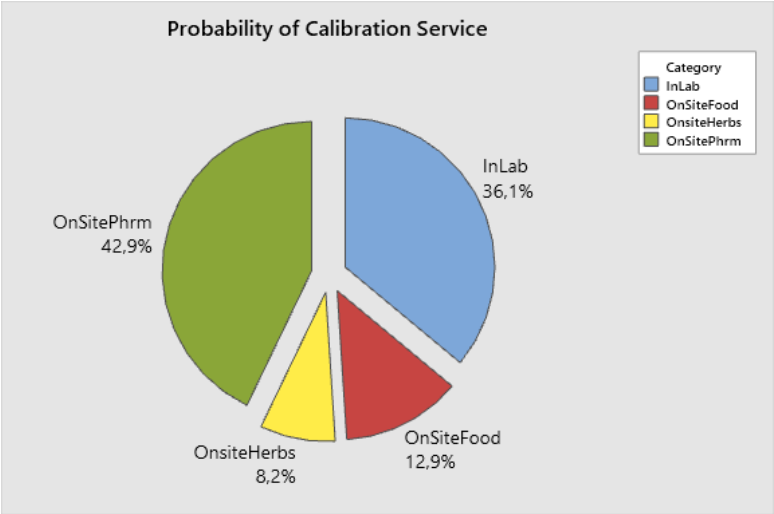

Figure 5. The Probability of Calibration Service

RESULT AND DISCUSSION

The system model was then created using the Promodel2016 software with a mimic model simulation as shown in Figure 6, with the parameters as shown in Table 1.

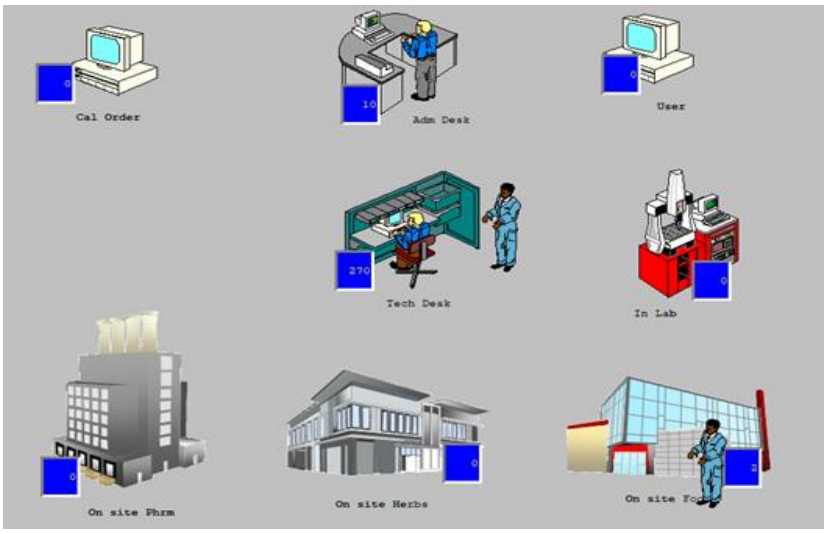

Figure 6. Digital Twin Model Simulation in Promodel2016 for Pharmaceutical Industry Calibration Service Case

Analysis of distribution fitting results from big data obtained from actual performance records of the Calibration Laboratory can be detailed in table 1 which then becomes input parameter data into the simulation model created in Promodel. Operation time and Moving Time where the activities are only scrolling and clicking at the electronic device can be assumed with uniform distribution at average 1 minute duration.

Table 1. Parameter set on the model simulation built from analyzed data value

Input			output			Probability	Operation time	Move time
Location	**Entities**	**Logic**	**Location**	**Entities**	**Logic**			
Cal Order	CalOrd	Random	Adm Desk	CalOrd	No queing	100%	E(0.1) min	0.1 min
Adm Desk	CalOrd	Random	Tech Desk	CalOrd	Random	100%	U(1,0.1) min	W(0.4,1084) min
TechDesk	CalOrd	Random	InLab	CalOrd	Random	36.1%	U(1,0.1) min	W(0.7,37759) min
TechDesk	CalOrd	Random	OnsitePhrm	CalOrd	Random	42.9%	U(1,0.1) min	W(0.6,31579) min
TechDesk	CalOrd	Random	OnsiteHerbs	CalOrd	Random	8.2%	U(1,0.1) min	W(1.0,45105) min
TechDesk	CalOrd	Random	OnsiteFood	CalOrd	Random	12.9%	U(1,0.1) min	W(0.9,43266) min
InLab	CalOrd	Random	Adm Desk	CalData	FIFO	100%	W(0.9,117) min	U(1,0.1) min
OnsitePhrm	CalOrd	Random	Adm Desk	CalData	FIFO	100%	W(0.9,202) min	U(1,0.1) min
OnsiteHerbs	CalOrd	Random	Adm Desk	CalData	FIFO	100%	W(1.1,165) min	U(1,0.1) min
OnsiteFood	CalOrd	Random	Adm Desk	CalData	FIFO	100%	E(229) min	U(1,0.1) min
Adm Desk	CalData	Oldest	User	CalCert	FIFO	100%	W(0.7,1832) min	EXIT

Simulation results using input parameters from actual events between January 2024 to April 2024 including the number of Calibration Orders (CalOrd) per month and the average hours used per technician per month can be presented in table 2. Number of Calibration Certificates (CalCert) produced each month is used as a benchmark for simulation data output. Simulation replication was carried out ten times.

The similarity test with the one sample t-test approach shows that the simulation results based on actual event data for 4 months can be justified that there is not enough evidence to conclude that the difference between the simulation model and the actual situation is statistically significant. The simulation model can be justified as a digital twin with system behavior which is a replica of the actual conditions of the Pharmaceutical Industry calibration service system.

Table 2. Verification of 10 replications Digital Twin Simulation model with actual event

Month	Nr of Technician	Total hour	CalOrd*	CalCert Output						
				Actual	10 Replications Digital Twin Simulation					95% confident interval
Jan-2024	4	194	350	315	325	306	315	327	346	307 to 333
					309	312	317	340	311	
Feb-2024	4	201	399	339	336	325	331	361	334	317 to 345
					332	309	339	355	321	
Mar-2024	4	196	367	340	343	324	333	360	332	331 to 351
					345	349	332	328	355	
Apr-2024	4	173	290	278	300	274	275	269	274	269 to 297
					271	297	292	275	287	

* Calibration Order cumulative for the actual month + past due at previous month

The results of the one sample t-test can be seen graphically in Figure 7 below.

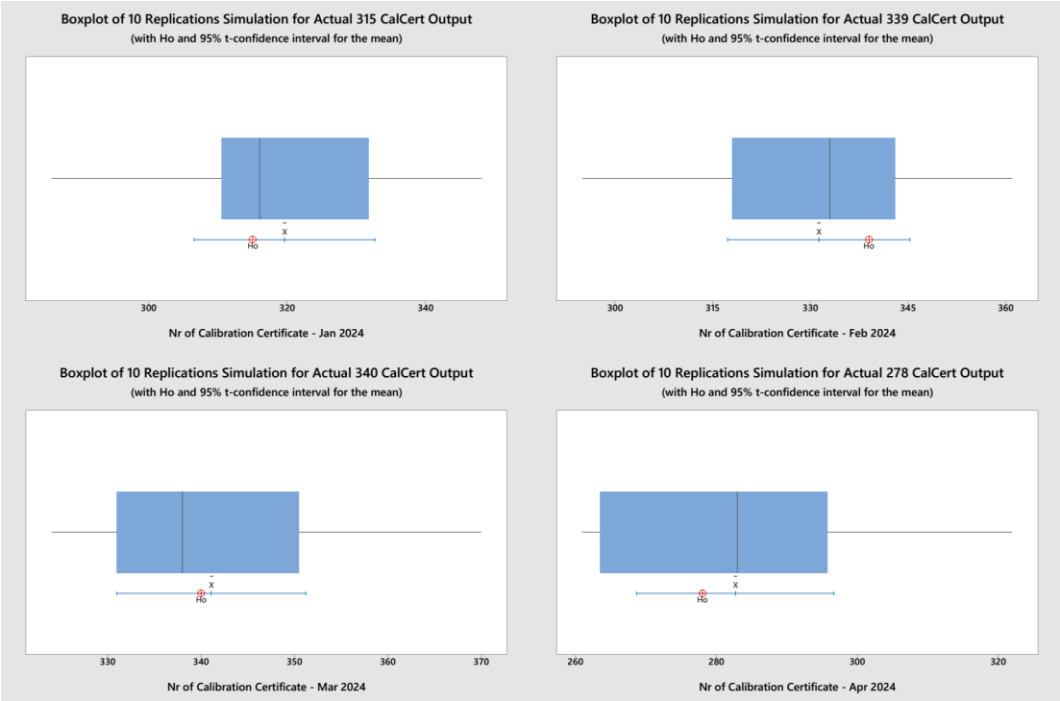

Figure 7. One sample t-test of Actual Event vs Digital Twin Simulation

CONCLUSION

Discrete event simulation theory using the Promodel2016 software application has proven capable of being used as a digital twin of real situations in Pharmaceutical Industry Calibration Laboratory Services. Simulation on digital twin can be used, among other things, to carry out various optimization scenarios on existing systems so that the output of calibration services (Calibration Certificates) can be maximized with minimizing the use of resources (including, minimizing the use of technician hours to avoid overtime, testing of increased calibration loads without having to add technicians, finding most efficient scenario predictions against increasing load of number of Calibration Order), without having to do it by trial and error at a real system.

Further research needs to be carried out to challenge the robustness of the digital twin's similarity as a system replica if changes occur outside the system boundary determined in this research. The case of calibration services in commercial laboratories also poses a challenge to prove whether this approach can help the laboratory to improve its performance.

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